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Rain
with chances of a Thunderstorm

On the role of anger in depression

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On the role of anger in depression

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Voor pp & mm

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General introduction

Depression

In the Netherlands, major depressive disorder (MDD) affects an estimated 15.4% of individuals during their lifetime (Bijl et al., 1998). This number is comparable with the reported lifetime prevalence of MDD in the United States, which is 16.2% (Kessler et al., 2003). The impact of depression on the individual and society is as big as that of common medical illnesses (Merikangas et al., 2007), making it an important target of research over the past decades. This research has resulted in extensive knowledge about the disease and how to treat it. However, this knowledge is still far from complete. For example, 50% of depressed patients react only partially or even not at all to antidepressant treatment (Souery et al., 2006). Moreover, about one third of depressed patients will in time become resistant to treatment (Fava and Davidson, 1996). One explanation for this hiatus may be that depression is a very heterogeneous disease. To be diagnosed with MDD, an individual has to fulfill five of the eleven criteria of a major depressive episode, as stated by the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV; American Psychiatric Association, 2001) (Table 1.) (The studies described in this thesis were all conducted before the introduction of DSM 5 in 2013).

Thus, theoretically, two patients can be diagnosed with MDD based on two entirely different symptom profiles. Identifying certain subtypes of MDD could contribute to differentiation and specification of treatment strategies, improving an individuals' likelihood of treatment-response and as such improving chances of remission (Wong and Licinio, 2001).

Subtypes of depression

At the end of the 19th century, Paul Julius Möbius further developed Morel's (1857; as cited in Mendels and Cochrane, 1968) theory of distinction between exogenous (caused by the environment) and endogenous (caused by heredity) psychiatric disorders (Möbius, 1893 as cited in Beer, 1996). This in turn inspired Kraepelin's dichotomization of endogenous depression (or 'manic-depressive psychosis') and exogenous or reactive depression (Kraepelin, 1913). In a review of seven studies that used factor analysis, Mendels and Cochrane (1968) confirmed the independence of endogenous and reactive factors, but proposed an alternative take on this dichotomy; the endogenous factor may represent a 'classical' depressive syndrome, whereas the reactive factor may reflect a (group of) psychiatric disorders where depression is only one of the symptoms (Mendels and Cochrane, 1968). In the early 70s of the 20th century, Akiskal and McKinney argued for the unification of these two types of depression, stating that depressive illness should be seen as the result of several processes that interact in brain areas associated with e.g. arousal, mood and motivation. These processes can be influenced genetically, developmentally, psychosocially, physiologically or by personality traits, eventually resulting in biochemical alterations, of which depression is one of the possible outcomes (Akiskal and

Table 1

DSM-IV criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

(1) *Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful).*

(2) *Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).*

(3) *Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), or increase or decrease in appetite nearly every day.*

(4) *Insomnia or hypersomnia nearly every day.*

(5) *Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).*

(6) *Fatigue or loss of energy nearly every day.*

(7) *Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).*

(8) *Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).*

(9) *Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.*

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not due to the direct psychological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition.

Mckinney, 1973, 1975). Shortly thereafter, in 1980, the unitarian model of depression was recorded in the newest version of the DSM-III (American Psychiatric Association, 1980). Not only etiologically is the distinction between endogenous and exogenous depression untenable, another difficulty is the notion that depressive disorder is a highly recurrent disorder. The risk of recurrence of depression increases from 50% after one's first episode to 80% after 2 or more episodes (Kupfer et al., 1996, Post, 1992). This suggests that even though a depression may initially be initiated by adverse life events, therefore being classified as exogenous, its occurrence then increases the risk of recurrence without further life events, turning into endogenous depression.

Besides diagnostic criteria, the DSM-IV describes three levels of classification of MDE: first, the clinical status of the current (or in case of (partial) remission most recent) depressive episode is defined. Besides level of remission (current episode, partly remitted, or fully remitted), description of the clinical status includes severity (mild, moderate, or severe). Severe depression can be further classified by absence or presence of psychotic symptoms. A second level of definition used by the DSM-IV-TR is based on the course of the disorder (the 'chronicity specifier') or on specific symptoms (catatonic features, melancholic features, atypical features, and postpartum onset). The third classification of depressive episodes according to the DSM-IV-TR is based on the characteristics of recurring episodes (longitudinal course specifiers and seasonal pattern).

Thus, in the DSM-IV, a subtype of depression is based on behavioral and course characteristics of depressive episodes. Other factors that may influence course and treatment success of the disease like gene polymorphisms or biomarkers are not considered.

Depression and anger regulation problems

Anger regulation problems, ranging from irritability and hostility to verbal and/or physical aggression, e.g. in the form of anger attacks, have long been associated with depression. This recognition dates back as far as Kraepelin, who already recognized the occurrence of anger as a symptom of depression (Kraepelin, 1883). According to Kraepelin, when the inner tension that comes with depression can no longer be restrained, release will be found in an uncontrolled act of aggression. This act can be directed towards oneself, resulting in suicide. When the fear of dying is too great, however, release can be sought in an act of aggression directed at others, even resulting in murder. Freud also recognized the concept of anger in the context of depression. He saw anger as something that could not only be expressed outwards, but can also turn inwards, resulting in depression (Freud, 1917). More recently, Van Praag suggested that aggression is one of the core symptoms of depression caused by 5-HT disturbance, and mood lowering is only a secondary symptom (Van Praag, 1992). Moreover, studies by Fava et al. confirmed that 30 to 40% of depressed patients report anger attacks (Fava and Rosenbaum,

1998, 1999). Moreover, irritable mood is considered a core symptom of depression in children and adolescents (American Psychiatric Association, 2001). However, in adult patients with depression, it is not part of the diagnostic criteria, despite the fact that about 30-40% of adult patients report symptoms of irritability and anger (Fava et al., 2009, Fava and Rosenbaum, 1999, Perlis et al., 2009, Fava and Rosenbaum, 1998). Antidepressant medication has been used successfully to reduce these symptoms (Van Praag, 2001, Katz et al., 1987).

In the early 90s of the 20th century, Van Praag proposed a subtype of depression which he called 'Serotonin-related, anxiety/aggression-driven, stressor-precipitated depression' (Van Praag, 1996). The primary symptoms of this subtype were not sadness and anhedonia, but anxiety and aggression. Evidence for this subtype came mainly from association studies, for example from a study showing higher anxiety scores for depressed patients with lower concentrations of the metabolite 5-Hydroxyindoleacetic acid (5-HIAA) which indicates lowered serotonin (or 5-hydroxytryptamine – 5-HT) turnover (Van Praag, 1998). The theoretical background of this subtype however remained rather unclear. An undefined combination of biological and psychological predisposition or impairment results in susceptibility to stress which in turn can cause increased risk of anxiety and suppressed anger, eventually resulting in depression (Van Praag, 1998, 1996).

Fava et al. investigated the differences between depressed patients with and without anger attacks (Fava et al., 1997, Fava and Rosenbaum, 1999, Fava et al., 1993). Anger attacks were defined as: 'sudden spells of anger accompanied by symptoms of autonomic activation such as tachycardia, sweating, hot flashes, and tightness of the chest which resembles panic attacks but without the predominant affects of fear and anxiety' (Fava and Rosenbaum, 1998). Depressed patients with anger attacks were found to differ from depressed patients without anger attacks, for example in their clinical profiles. Specifically, depressed patients with anger attacks had higher levels of hostility and anxiety (Fava et al., 1993) and more comorbid axis II psychopathology (Tedlow et al., 1999) compared to depressed patients without anger attacks. Physiological differences were also observed between these patient groups, with depressed patients with anger attacks having higher cholesterol levels and an increased risk of cardiac dysfunction (Fraguas et al., 2007) compared to depressed patients without anger attacks.

A milder form of anger regulation problems in depression -irritability- was also found to be present in about 40% of depressed patients (Fava et al., 2009, Perlis et al., 2009). These irritable depressed patients reported an 'irritable, grouchy or […] bad mood almost every day during the worst two weeks of the index [depressive] episode' (Fava et al., 2009). Comparing depressed patients with and without irritability, those with irritability had a higher number of aggression-related axis II disorders (Fava et al., 2009), reported symptoms of dysthymia more often (Perlis et al., 2009), and had a greater prevalence of comorbid anxiety disorders (Fava et al., 2009, Perlis et al., 2009). Irritable depressed patients had also more often attempted suicide

(Perlis et al., 2009) than depressed patients who were not irritable during their depression. Based on the aforementioned studies, anger attacks and irritability might be characteristics to distinguish different types of depression from each other.

Factors contributing to depression & anger/aggression

Maladaptive behavioral patterns such as depression and aggression generally do not have one specific cause. Rather, numerous factors can contribute to the onset and relapse of depression and aggression, and some, if not all of them might interact. Literature on factors associated with depression and aggression is further discussed below.

Serotonin

An important aspect of depression is its association with 5-HT; more specifically, impairments of the 5-HT system have been found relatively consistently in depression (Maes and Meltzer, 1995). Animal models (Sanchez and Meier, 1997), post-mortem studies in suicide victims (Åsberg et al., 1976) as well as the beneficial effect of serotonin reuptake inhibitors (SSRI's) in large numbers of depressed patients (Trivedi et al., 2006, Willner et al., 2013) support this hypothesis.

The first studies to investigate 5-HT neurotransmission in depression experimentally included so-called 5-HT neuroendocrine challenge tests. An example of such a neuro-endocrine challenge test that was commonly used up to the late 1990s, included the administration of thyrotropin releasing hormone (TRH) or DL-fenfluramine hydrochloride (Jans et al., 2006). 5-HT inhibits the release of thyrotropin releasing hormone (TRH), a hormone that normally stimulates the release of prolactin. Fenfluramine is a 5-HT releasing agent and re-uptake inhibitor (Mcbride et al., 1990) which increases plasma prolactin in healthy volunteers (Cowen, 1993) through the activation of 5-HT2a/2c receptors. Compared to depressed patients without anger attacks, depressed patients with anger attacks showed blunted prolactin response to both TRH and fenfluramine (Fava et al., 2000, Rosenbaum et al., 1993), as well as an increased response to the selective serotonergic reuptake inhibitor (SSRI) fluoxetine (Rosenbaum et al., 1993). Another study with fluoxetine reports no significant differences in the improvement of depressive symptoms after fluoxetine intake between depressed patients with anger attacks and depressed patients without anger attacks (Fava et al., 1993).The only study to investigate the use of antidepressant medication as a treatment of anger attacks found that sertraline (an SSRI) and imipramine (a tricyclic antidepressant or TCA) were more effective than placebo in reducing the anger attacks in depressed patients (Fava et al., 1997).

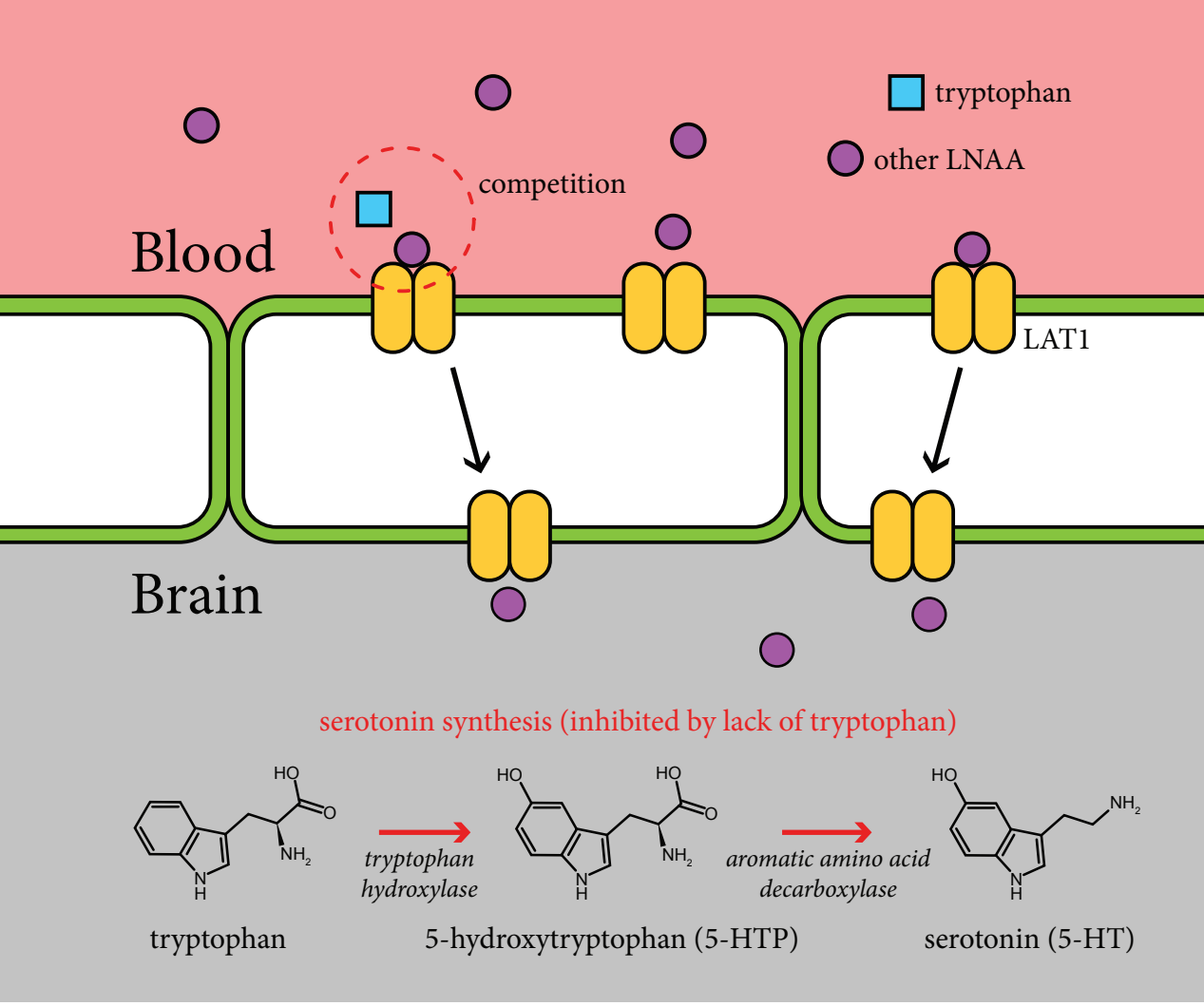

Figure 1. Acute Tryptophan Depletion (ATD)

Normally free tryptophan (Trp) is transported through the blood brain barrier (BBB), as are other large neutral amino acids (LNAAs), after which it is converted via 5-hydrxytryptophan (5-HTP) into serotonin (5-HT). ATD consists of LNAAs without the addition of Trp, resulting in increased competition at the BBB, resulting in less available free Trp in the brain and subsequently lower levels of 5-HT.

Acute tryptophan depletion

While the 5-HT hypothesis of depression in its original formulation postulated 5-HT impairments as the cause of depression, this hypothesis has been refined over the years (Booij et al., 2013). One specific procedure that has been used extensively to investigate the role of 5-HT in depression, and in fact contributed to the refinement of the 5-HT hypothesis of depression, is acute tryptophan depletion (ATD). This method temporarily lowers the precursor of 5-HT, the amino acid L-tryptophan (Trp) in the brain (Young et al., 1985, Van der Does, 2001) (Figure 1). Normally, Trp is taken up from the blood. Most of the Trp in the blood is protein-bound, but the 5% that is not is called free Trp which is transported across the blood-brain barrier, where it competes with five other large neutral amino acids (LNAA's: valine, leucine, isoleucine, phenylalanine and tyrosine) (Young et al., 1985). In the brain, Trp is converted into 5-HT. ATD in humans consists of the intake of a mixture of LNAA's. These LNAA's promote protein synthesis and compete with Trp at the blood-brain barrier, eventually causing decreased Trp levels in the brain, which in turn causes lowering of 5-HT synthesis. ATD therefore allows the investigation of the causal effects of lowered serotonin neurotransmission on human behavior in a controlled experimental design (Young et al., 1985).

Numerous studies have investigated the effects of this transient lowering of 5-HT on depressed mood. The first ATD studies in depression showed that remitted depressed patients using SSRIs have a greater increase in depressive symptoms in response to ATD than those using monoamine oxidase inhibitors or TCAs (Delgado et al., 1990, Delgado et al., 1999). Participants who were recovered and symptom-free (Smith et al., 1997) showed an increase in depressive symptoms in reaction to ATD relative to placebo, as did healthy individuals with an extensive family history of depression (Benkelfat et al., 1994). In currently depressed patients, no immediate effect of ATD on depressive symptoms was found (Delgado et al., 1994, Booij et al., 2005,). Moreover, in remitted/recovered depressed patients, a greater response to ATD has been associated with recurrent past episodes, female gender, history of suicidal ideation (Booij et al., 2002), certain genotypes of specific 5-HT genes (Neumeister et al., 2006) and impaired 5-HT2A receptor function (Yatham et al., 2012). These studies, in combination with other challenge studies in vulnerable populations (e.g. Bhagwagar et al., 2002) suggest that impaired 5-HT function in depression might be an indication of someone's vulnerability to depression rather than a direct cause of depression (Booij et al., 2003, Willner et al., 2013, Booij et al., 2013).

5-HT and aggression

In addition to vulnerability to depression, impaired 5-HTergic function has also been associated with a range of vulnerability to aggression-related behaviors, such as impulsive

and violent criminal behavior (Marsh et al., 2002), suicide attempts (Åsberg et al., 1976), physical aggression (Booij et al., 2010), and completed suicides (Träskman-Bendz and Mann, 2001). Cleare and Bond (1995) found increased anger, aggression, annoyance and hostility after ATD in healthy males with high trait aggression compared to healthy males with low trait aggression.

Antidepressant treatment and aggression

The Multidisciplinary Guideline for Depression (MDRL; Spijker et al., 2013) provides recommendations and instructions of operation for use in daily practice of mental health care for depression in adults. When the use of antidepressant medication is indicated, e.g. for moderate to severe depression and depression with melancholic or psychotic symptoms, the MDRL recommends the use of SSRIs for all outpatients. Anderson et al. (1998, 2000) showed that TCAs were only more effective compared to SSRIs in inpatients, which is however not necessarily related to depression severity (Anderson, 2000).

The SSRI fluoxetine has also been shown to reduce irritability and aggression scores in patients with personality disorder (Coccaro and Kavoussi, 1997). Together with recommendations from previous studies on anger regulation problems in depression (Van Praag, 2001, Katz et al., 1987, Fava et al., 1993, Rosenbaum et al., 1993) it seems for depression with anger regulation problems SSRIs may be preferable.

Figure 2 is based on the MDRL and shows the potential use of anger regulation problems in diagnostic decisions for treatment of depression. In line with the 'profiling' concept to identify characteristics that influence the course of depression and/or treatment outcome, anger regulation problems may have a place in diagnostic and treatment related decisions.

Cognition

In addition to depressed mood, and symptoms of irritability, anger and/or aggression in some subgroups of depressed patients, cognitive impairments often occur in depression. Concentration and memory problems are part of the diagnostic criteria of MDD (DSM-IV; American Psychiatric Association, 2001). Moreover, it has been shown that depressed patients show a bias towards negative information in various emotion processing tasks (Gur et al., 1992, Burt et al., 1995, Bouhuys et al., 1999, Elliott et al., 2011, Gotlib and Mccann, 1984, Gollan et al., 2008, Mikhailova et al., 1996, Segal et al., 1995, Surguladze et al., 2004). This bias might persist after remission from depression (Bhagwagar et al., 2004, de Raedt and Koster, 2010, Hayward et al., 2005, Joormann and Gotlib, 2007). Merens et al. (2008b) found some persisting bias for emotional stimuli such as fearful faces in a sample of remitted depressed

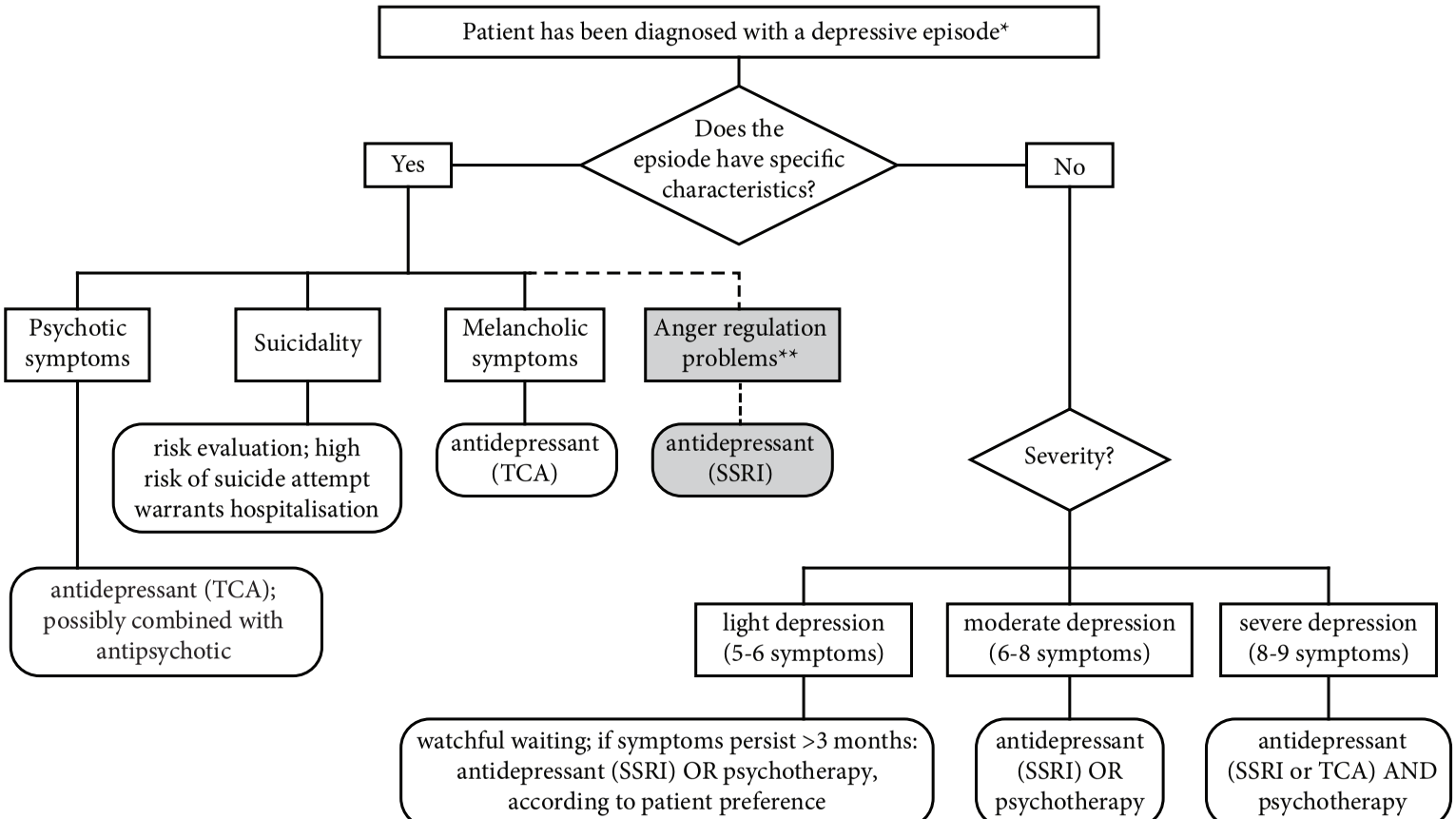

Figure 2. The potential place of anger regulation problems in diagnostic decision making in depression.
(based on the Multidisciplinary Guideline for Depression; Spijker et al., 2013)
TCA: Tricyclic antidepressant; SSRI: selective serotonin reuptake inhibitor

patients. However, their study suggests that most biases found during the depression may have become latent after remission, and will only be activated after being triggered, for example by ATD. Studies using this technique found evidence for a causal role of 5-HT in these emotional biases in both healthy volunteers (Munafò et al., 2006, Elliott et al., 2011) and remitted/recovered depressed patients (Hayward et al., 2005, Booij et al., 2005, Merens et al., 2008a).

Depressed patients often have dysfunctional cognitive schemas (Beck, 1967), with thoughts such as 'People will probably think less of me if I make a mistake' (Weissman, 1980, Weissman and Beck, 1978). These so-called dysfunctional attitudes merely become inactive instead of actually disappearing during remission (Teasdale, 1988). The ease, with which these latent dysfunctional schemas are reactivated in response to sad mood, is called cognitive reactivity (Segal et al., 1999). Several studies have shown that remitted depressed patients have significantly higher cognitive reactivity levels than never-depressed healthy individuals (Miranda and Persons, 1988, Van Der Does, 2002, de Raedt and Koster, 2010). High levels of cognitive reactivity predicted relapse to depression within four years after treatment (Segal et al., 1999). Moreover, in remitted depressed patients, a greater mood response to ATD was associated with greater cognitive reactivity (Booij and Van Der Does, 2007), thereby showing a possible link between cognitive and 5-HT vulnerability.

Psychophysiology

Several changes in neuroendocrine measures have been associated with depression and aggression/anger. For example, increases in testosterone and cortisol have been associated with aggression (Harris, 1999, Van Bokhoven et al., 2005). Anger problems in MDD have also been associated with increased cortisol levels (Van Praag, 2002, Van Praag, 1996a). Moreover, increased testosterone has frequently been linked to anger and aggression regulation (Persky et al., 1971, Van Honk et al., 1999, Archer, 2006, Mehta and Beer, 2009).

Both cortisol and testosterone have been shown to interact intensively with the 5-HT system (Cowen, 2002, Strickland et al., 2002, Way and Taylor, 2010, Kuepper et al., 2010, Montoya et al., 2012). On the other hand, diminished testosterone levels have been found in female depressed patients (Giltay et al., 2012). Moreover, patients using SSRIs had higher levels of testosterone than those not using SSRIs (Giltay et al., 2012). Administration of testosterone has been suggested to have antidepressant effects in some patients such as older depressed males (Zarrouf et al., 2009). However, randomized controlled trials are lacking.

Depressed patients are more vulnerable to cardiovascular disease (CVD) than non-depressed individuals (Joynt et al., 2003). Lowered heart rate variability (HRV) has been identified as a

possible risk factor for CVD and several studies did find lowered HRV in depressed patients (Agelink et al., 2002, Rechlin et al., 1994). Moreover, in a study which compared remitted depressed patients who reported suicidal ideation during their depression with remitted depressed patients without previous suicidal ideation, Booij et al. (2006) found that ATD significantly lowered HRV in remitted depressed with previous suicidality but not in those without. This suggests that depressed patients with previous suicidal ideation may have an increased risk of CVD which is possibly associated with increased 5-HTergic vulnerability (Booij et al., 2006).

Another CVD risk factor associated with depression, suicide and aggression is cholesterol levels. Lowered serum cholesterol was found for MDD patients compared to healthy controls (Olusi and Fido, 1996, Lehto et al., 2008, Steegmans et al., 2000, Shin et al., 2008) as well as in suicide attempters compared to nonsuicidal psychiatric patients (Kunugi et al., 1997, Troisi, 2009). A study by Buydens-Branchey et al. (2000) suggested that the link they found between lowered cholesterol and poor impulse-control and aggression may be associated with alterations in 5-HT function.

In sum, several neuroendocrine and psychophysiological indices are associated with depression and aggression, and all of those measures have to some extent been associated with 5-HTergic functioning.

Heritability

Depression is known to occur more frequently in individuals with a family history of depression (Kendler et al., 1997, Sullivan et al., 1996, Sullivan et al., 2000) compared to those without a family history of depression. Comparing monozygotic and dizygotic twins and adoption studies have enabled us to disentangle the role of genetic and environmental influences on the development of psychopathology. Several longitudinal twin studies have found moderate heritability rates of depression of 42% in women and 29% in men (Kendler et al., 2006, Kendler et al., 2001, Bierut et al., 1999, Jansson et al., 2004).

Candidate gene studies have been done in an attempt to identify specific genes involved in depression. Many of these are linked to the 5-HT system, although many other genes of other biological systems have been identified, and all of them might interact (Lesch, 2004). Below is a description of the most commonly studied candidate genes in the context of depression, aggression and suicidality.

5-HT transporter gene (SLC6A4)

Probably the most widely investigated polymorphism in psychiatry is the 5-HT transporter (5-HTT) linked polymorphic region (5-HTTLPR) of the SLC6A4 gene (Risch et al., 2009, Lesch, 2004) and its association with depression. Function of SLC6A4, involved in 5-HT uptake in the brain, is known to be altered in several disorders e.g. depression, as well as bipolar disorder and schizophrenia (Heils et al., 1996). SLC6A4 is also a prime target for antidepressant action (Heils et al., 1996). The most commonly investigated polymorphism of the 5-HT transporter, 5-HTTLPR, has two variants. The short allele (s) variant results in reduced transcriptional efficiency compared to the long allele (l). More recently, another polymorphism (rs25531) has been described (Wendland et al., 2006). This G allele in the l variant of the polymorphism is functionally similar to the s allele, with lower 5-HTT mRNA expression (Hu et al., 2006). Carriers of at least one s allele have a higher risk of depression and increased anxiety-related traits (Lesch et al., 1996a) compared to homozygote long allele carriers (ll). Comparing depressed and non-depressed women, Gonda et al. (2011) found an association between the s allele and aggression/hostility, which was even more marked in the presence of depression. One psychological concept extensively studied in relation to depression is neuroticism: the tendency to more easily experience negative emotions, including feelings of depression, anxiety and anger (Matthews et al., 2003). Lesch et al. found increased levels of anxiety associated with the s allele (Lesch et al., 1996b). In another study in healthy women, the s allele was associated with traits and characteristics related to the concept of neuroticism, e.g. anxiety, depression, hopelessness and hostility (Gonda et al., 2009).

However, the findings are not consistent. As Levinson (2006) already pointed out, the positive associations between depression and 5-HTTLPR found by previous studies are mostly small and indirect. The meta-analysis by Karg et al. (2011) found evidence of increased stress sensitivity in association with the s allele of the 5-HTTLPR polymorphism, whereas two meta-analyses by Munafò et al. (2009) and Risch et al. (2009) found no such association. The inconsistency between these studies may partly be explained by methodological differences between studies used in these meta-analyses (Uher et al., 2010).

5-HT1A receptor gene

The 5-HT1A receptor is a 5-HTergic autoreceptor in the raphe; it is also expressed post-synaptically in other brain-regions. It is involved in the regulation of 5-HT transmission by reduction of firing rate through negative feedback; one relatively common variant (Wu and Comings, 1999) of this receptor (C-1019G) has been shown to lead to a decrease in 5-HT transmission (Lemonde et al., 2003, Neumeister et al., 2004) and has been linked to major depression and suicide to (Lemonde et al., 2003, Kishi et al., 2013). Although the observation of the relationship between the G-allele of the 5- HT1A C(-1019G) gene and MDD has been

replicated (e.g. Albert et al., 2011), findings have not been entirely consistent (e.g. Arias et al., 2002), as is the case for all other candidate gene studies in MDD.

Tryptophan hydroxylase

Tryptophan hydroxylase (TPH) is a rate-limiting enzyme which is critical for the biosynthesis of 5-HT – converting the amino acid Trp to 5-hydroxytryptophan (5-HT) which in turn is decarboxylated into 5-HT (Bondy et al., 2006). Two forms of TPH exist; TPH1 is found mainly peripherally, whereas another variant (now called TPH2) is found only in the brain (Zhang et al., 2004). One study showed that genotypic variation in several TPH2 polymorphisms in humans predicted individual variation in brain serotonin synthesis in frontal limbic regions vivo, using Positron Emission Tomography (Booij et al., 2012), supporting the relevance of this gene for controlling brain 5-HT synthesis in humans in brain regions involved in emotion regulation.

The TPH1 gene has two common polymorphisms in intron 7 consisting of an A to C substitution at nucleotides 779 (A779C) and at 218 (A218C) which are in tight, but not complete, linkage disequilibrium. Literature on the association between variation in the TPH1 gene and depression or aggression/suicidality is inconsistent (Lalovic and Turecki, 2002, Bellivier et al., 2004).

Since TPH2 is expressed only in the brain, the TPH2 gene (located on chromosome 12q15) is arguably a more promising candidate gene to investigate the association between TPH and suicidality, aggression and depression (Bondy et al., 2006). Variations in TPH2 polymorphisms have previously been associated with MDD, suicide, anxiety and hyperactivity (Booij et al., 2012). Moreover, TPH2 haplotype linkage to anxiety/depression phenotypes and suicide attempts bas been identified in 2 different populations (Zhou et al., 2005, Zill et al., 2004). However, many inconsistencies in the literature still occur.

MAOA gene

The MAOA gene was associated with aggression in the early 2000s in the Dunedin study (Silva and Stanton, 1996, Arseneault et al., 2000, Caspi et al., 2003) and has since been identified as the 'warrior gene' in popular media. The monoamine oxidase A (MAOA) gene has been studied mainly in association with aggression. MAOA is an enzyme essential for the degradation of monoamines in the central nervous system (Oreland, 1991). The MAOA gene is located on the X chromosome (Xp11.23-11.4) and one of the most investigated variations is that of a variable number of tandem repeats (VNTR). Alleles with 3.5 or 4 copies lead to

2-10 times more efficient transcriptional activity (indicating high expression; MAOA-H) than alleles with 3 copies (low expression; MAOA-L) (Sabol et al., 1998).

The MAOA enzyme has both been linked to aggression and to the development and pharmacological treatment of depression (Aklillu et al., 2009, Pare, 1985). Recently, variations in other polymorphisms than the VNTR were also found to be related to levels of anger expressed outwards by male and female suicidal patients (Antypa et al., 2012) (63.7% of which were patients with affective disorder).

Gene by environment interaction

Although the examples given indicate that variants of certain polymorphisms may predispose to depression and aggression, the putative vulnerability of carrying a certain variant may especially be expressed in the presence of adverse events, e.g. childhood maltreatment or stressful life events.

For example, the association between stressful life events and depression was stronger in carriers of at least one s allele of the 5-HTTLPR compared to ll homozygotes (Caspi et al., 2003). Null findings have also been reported, although a meta-analysis confirmed this association (Karg et al., 2011), and some of the non-significant studies appear to be attributed to less rigorous methodology.

Childhood maltreatment can result in symptoms of depression as well as antisocial behavior later in life; however, MAOA-H carriers seem less likely to develop antisocial behavior after childhood maltreatment than MAOA-L carriers (Caspi et al., 2002). Little is known about gene by environment interactions of other commonly studied 5-HT genes associated with depression.

Research aims & outline of this thesis

This thesis investigates the significance of anger regulation problems in the context of depression. Both depression and aggression have been studied extensively, but although 30-40% of depressed patients may have aggression problems, reports on the significance and implications of their co-occurrence are limited. Aggression as well as depression have been associated with some similar biological mechanisms (5-HT, genetic, neuroendocrine, and psychophysiological). This thesis may shed some light on the extent to which the presence of anger regulation problems represents a putative subtype of depression, possibly guiding treatment preferences as well.

In Chapter 2, we compare currently depressed patients reporting irritability to those not reporting irritability in terms of clinical and demographic characteristics. For this comparison, we use data from the Netherlands Study of Depression and Anxiety (NESDA), from which we selected the 913 participants who met the criteria for major depression, minor depression, or dysthymia during the month prior to study admission. We compare those with and without irritability on clinical features, psychological characteristics and physiological measures.

Heritability appears to contribute to the development of psychopathology, and heritability of both depression and aggression has been studied extensively. However, little is known on the heritability of aggression regulation problems in the context of depression. The aim of Chapter 3 is to investigate a possible genetic mechanism for the occurrence of aggression in the context of depression. To investigate this, we specifically focus on the association between monoamine oxidase A (MAOA) genotypic variation and aggression, especially in well-documented interaction with childhood trauma (Caspi et al., 2002, Kim-Cohen et al., 2006, Haberstick et al., 2005). To investigate the role of the MAOA gene in aggression in the context of depression, we test whether the low expression variant is associated with trait and state measures of anger and measures of aggression including cognitive reactivity to sad mood.

Since both depression and aggression have repeatedly been associated with lower 5-HT neurotransmission, our next step is to investigate 5-HTergic vulnerability in aggression in the context of depression. Specifically, given the association with lower 5-HT neurotransmission, we investigat whether patients with depression and aggression problems have more impairment in the 5-HT system compared to patients without aggression during depression using ATD. Chapters 4 and 5 discusses the results of this experimental study we conducted, where remitted depressed patients with (MDD+A) and without (MDD-A) anger problems during their depression participated in an acute tryptophan depletion (ATD) study. In Chapter 4, we examine differences in depressive symptom reactivity in response to ATD between remitted depressed patients with (MDD+A) and without (MDD-A) anger regulation problems during their depression. We also investigate testosterone and cortisol responses, two hormones implicated in both in depression as well as aggression. In Chapter 5, we investigate differences in cognition between the MDD+A and MDD-A group; more specifically, we investigate whether depression with anger regulation problems is associated with increased impulsivity compared to depression without anger regulation problems. Moreover, we investigate differences in recognition of and reaction to emotional faces.

A summary of chapters 2-5 and a General Discussion of the studies in this thesis are given in Chapter 6.

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Chapter 2
Clinical and physiological correlates of irritability in depression: results from the Netherlands study of depression and anxiety

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Abstract

Objective: Irritable and non-irritable depressed patients differ on demographic and clinical characteristics. We investigated whether this extends to psychological and physiological measures.

Method: We compared irritable and non-irritable unipolar depressed patients on symptomatology, personality, and (psycho)physiological measures (cortisol, cholesterol, and heart rate variability). Symptomatology was reassessed after one year, and we also compared depressed patients who were irritable or non-irritable at both time points (Irr++ versus Irr−−).

Results: Almost half (46%; N = 420) of the sample was classified as irritable. These patients scored higher on depression severity, anxiety, hypomanic symptoms, and psychological variables. No differences were observed on physiological markers after correction for depression severity. The same pattern was found when comparing Irr++ and Irr−− groups.

Conclusion: Irritable and non-irritable depressed patients differ on clinical and psychological variables, but not on the currently investigated physiological markers. The clinical relevance of the distinction and the significance of the hypomanic symptoms remain to be demonstrated.

Introduction

Not all symptoms that are prevalent in major depression are part of its diagnostic criteria (American Psychiatric Association, 2001). For instance, most depressed patients experience significant levels of anxiety. Irritability is also reported by many. In children, irritability is the most common symptom of depression (Crowe et al., 2006) and is one of the diagnostic criteria. Two recent studies have examined the clinical significance of irritability in depression in adults. In a community sample of depressed patients, approximately half of the 955 patients with lifetime unipolar depression were also irritable during their worst episode (Fava et al., 2009), as measured with one item of the Composite International Diagnostic Interview. Depressed patients scoring positive on irritability had a younger age of onset and higher rates of comorbid attention-deficit/hyperactivity disorder, oppositional-defiant disorder, intermittent explosive disorder, dysthymia and anxiety disorders (Fava et al., 2009). A second study (Perlis et al., 2009) compared depressed patients with and without irritability based on the irritability item of a standardized symptom interview. Irritable depressed patients (N = 1, 067; 46%) reported more anxiety, loneliness and annoyance by daily hassles, and more prior suicide attempts than non-irritable depressed patients. Previous research by the same group focused on a depression subtype characterized by the presence of anger attacks, in other words by disturbances in the regulation of irritability (Fava et al., 1990, Fava and Rosenbaum, 1998, 1999). Around 40% of depressed outpatients had one or more anger attacks during the past month (Fava et al., 1997, Fava et al., 1993). In comparison with depressed patients without anger attacks, these patients had higher levels of hostility, anxiety, somatization (Fava et al., 1993), higher cholesterol levels (Fraguas et al., 2007), more axis II psychopathology (Tedlow et al., 1999), increased risk of cardiac dysfunction (Iosifescu et al., 2007), and a younger age of depression onset (Alpert et al., 2003). Depressed patients with anger attacks also showed a blunted response to the serotonin (5-HT) agonist fenfluramine (Fava et al., 2000). Compared to healthy controls, depressed patients with anger attacks showed differential activation of orbitofrontal–limbic circuits following an anger induction task (Dougherty et al., 2004). It has been suggested that irritability may also be a feature of unrecognized bipolar (spectrum) disorder (Benazzi, 2003, 2010, Benazzi and Akiskal, 2005). It has not been investigated yet to what extent irritability during a depressive episode predicts the development of bipolar disorder. However, other features of bipolar disorder, such as early age of onset, suicidality, family history, greater episode recurrence, and atypical depression were not found to be more common in the irritable depressed (Perlis et al., 2009). The present study had two aims. The first aim was to investigate whether the psychological and biological profile that has been found for depressed patients with anger attacks also applies to depressed patients with irritability. We compared outpatients with irritable and non-irritable unipolar depression on demographic, clinical, psychological, and biological markers that had previously been associated with impulsivity, aggression, or anger attacks. These markers include personality, cognitive reactivity, heart rate variability (Iosifescu et al., 2007), cholesterol (Fraguas et al.,

2007), and cortisol (Van Praag, 1996a). We hypothesized that depressed patients reporting irritability would score higher on anxiety and suicidality, lower on agreeableness, and higher on aggression reactivity. We also expected that irritable depression would be associated with lower heart rate variability, lower cholesterol concentrations, and higher levels of cortisol, particularly the cortisol awakening rise. The second aim was to investigate the association of irritability in depression with features of (hypo-)mania. For this, we measured (hypo-)manic symptoms in the same patients.

Methods

Participants

Participants were selected from the Netherlands Study of Depression and Anxiety (NESDA). This cohort study follows 2,981 adult participants over the course of 8 years (Penninx et al., 2008). NESDA respondents were recruited from the community and through primary and secondary care facilities. The total NESDA sample contains 2,329 individuals with a lifetime diagnosis of depression, dysthymia and/or an anxiety disorder, and 652 healthy participants. Participants with a diagnosis of bipolar disorder, a psychotic disorder, obsessive compulsive disorder, or severe addiction disorder are excluded from NESDA. For the present study, we selected the 913 participants who met the criteria for major depression, minor depression, or dysthymia during the month prior to study admission.

Instruments

Diagnoses

Current and past DSM-IV diagnoses of mood disorders, anxiety disorders, and alcohol abuse and dependency were assessed with the Composite International Diagnostic Interview (CIDI) (Robins et al., 1988). The interviews were conducted and scored by trained and supervised clinical research staff. Psychotic disorders and addictions were assessed in an open interview and checked in the medical records. Severity of alcohol dependence and abuse was assessed with the Audit questionnaire (Babor et al., 1989).

Symptomatology

Severity of depression during the past week was defined as the total score on the Inventory of Depressive Symptomatology (IDS-SR) (Rush et al., 1996), excluding the irritability item. Anxiety symptoms were assessed with the Beck Anxiety Index (BAI) (Beck et al., 1988). The BAI measures the somatic and cognitive aspects of anxiety during the past week (e.g.,

"numbness or tingling" and "fear of the worst happening"). It contains 21 items, scored on a four-point scale. The symptoms of bipolar disorder were assessed with the Mood Disorder Questionnaire (MDQ) (Hirschfeld et al., 2003), which contains 13 items derived from DSM-IV criteria and clinical experience (e.g., "you were so irritable that you shouted at people or started fights or arguments" and "you felt more self-confident than usual").

Irritability

Irritability status was determined using one item from the Inventory of Depressive Symptomatology— Self-Report (IDS-SR) (Rush et al., 1996). This item asks whether the participant has been "feeling irritable during the past seven days". The answers are scored on a four-point scale with descriptors "not feeling irritable" (1), "feeling irritable less than half the time" (2), "feeling irritable more than half the time" (3), or "feeling extremely irritable nearly all of the time" (4). The sample was split into low (scoring 1 or 2) (Irr−) and high irritable groups (scoring 3 or 4) (Irr+). The validity of this criterion has been shown previously in other cohorts (Fava et al., 2009, Perlis et al., 2009), but since the IDS measures past week severity only, irritability was reassessed at a one-year follow-up. This allowed us to create somewhat more extreme subgroups of depressed patients who were irritable both at baseline and at one-year follow-up (Irr++) and patients who were non-irritable on both assessments (Irr−−).

Suicidality

Previous suicide attempts were assessed with the Beck scale for suicide ideation (Beck and Beamesderfer, 1974).

Psychological Variables

Cognitive vulnerability to depression was measured with the Leiden Index of Depression Sensitivity—Revised (LEIDS-R) (Van Der Does, 2002, Williams et al., 2008). The LEIDS-R, a 34- item self-report scale, measures cognitive reactivity to sad mood on the following subscales: hopelessness/suicidality, acceptance/coping, aggression, control/perfectionism, risk aversion and rumination. Personality traits were assessed with the short form of the NEO Five Factor Inventory (NEOFFI) (Costa and Mccrae, 1995).

Table 1

Demographic and clinical characteristics of low and high irritable depressed patients – univariate results

	Low-irritable (N = 493)	**High-irritable (N = 420)**	
Demographic features			
Age (mean±SD)	43.4 ± 12.3	40.7 ± 11.7	η^2 = .012
Sex (% female)	65.9	65.7	OR = 0.99 (CI:0.75-0.30)
Recruited from:			
Specialized mental health care (%)	45.2	58.6	OR = 1.71 (CI:1.32-2.23) **
Community + primary care (%)	54.8	41.4	
Clinical features			
Age of Onset (mean±SD)[‡]	28.6 ± 13.1	26.6 ± 12.2	η^2 = .006 *
Smoking (% yes)	43.4	48.1	OR = 1.21 (CI:0.93-1.57)
Alcohol (% recent abuse and/or dependence)	8.5	8.1	OR = 0.95 (CI:0.59-1.52)
Comorbid anxiety (CIDI diagnosis %)	73.6	80.2	OR = 1.45 (CI:1.06-1.99) *
GAD (%)	24.9	36.7	OR = 1.74 (CI:1.31-2.31) **
Panic disorder (%)	22.7	37.1	OR = 2.01 (CI:1.51-2.68) **
Social phobia (%)	26.2	39.0	OR = 1.82 (CI:1.37-2.39) **
IDS total score (mean±SD)[a]	27.8 ± 10.1	37.7 ± 9.5	η^2 = .204 **
First degree family history with depression (%)	84.4	85.0	OR = 1.05 (CI:0.73 -1.51)
Beck Anxiety Inventory (mean±SD)	15.8 ± 9.4	23.8 ± 11.4	η^2 = .128 **
Suicidality (% ≥ 1 attempt during lifetime)	17.4	25.2	OR = 1.60* (CI:1.16-2.20)

Table 1 (Cont.)

	Low-irritable (N = 202)	High-irritable (N = 138)		
MDQ (% yes)				
Elated mood	28.8	32.0	OR = 1.20 (CI: 0.88-1.64)	
Increased self-confidence	39.4	39.9	OR = 1.02 (CI: 0.76-1.37)	
Less sleep needed	42.0	44.0	OR = 1.09 (CI: 0.81-1.45)	
More and/or faster speech	50.7	57.5	OR = 1.34 (CI: 1.01-1.79)	*
Racing thoughts	75.6	84.5	OR = 1.84 (CI: 1.27-2.68)	*
Concentration problems	74.6	85.3	OR = 2.06 (CI: 1.41-3.00)	**
More energy	44.6	45.7	OR = 1.06 (CI: 0.80-1.42)	
Increased activity	49.8	48.7	OR = 0.98 (CI: 0.73-1.30)	
Heightened sociability	23.9	28.4	OR = 1.27 (CI: 0.92-1.76)	
Increased libido	29.1	32.8	OR = 1.20 (CI: 0.88-1.64)	
Risk-taking	25.8	32.8	OR = 1.41 (CI: 1.03-1.93)	
Financial risk-taking	13.4	18.2	OR = 1.45 (CI: 0.98-2.14)	
[b]NEO FFI (mean±SD)				
Neuroticism	40.6 ± 6.6	45.2 ± 6.1	$\eta^2 = .009$	*
Extraversion	33.9 ± 6.7	31.1 ± 6.6	$\eta^2 = .001$	
Openness	31.1 ± 5.0	30.1 ± 6.0	$\eta^2 = .003$	
Agreeableness	43.5 ± 5.1	41.0 ± 5.6	$\eta^2 = .022$	**
Conscientiousness	35.3 ± 6.2	34.3 ± 6.3	$\eta^2 = .001$	

Table 1 (Cont.)

	Low-irritable (N = 427)	High-irritable (N = 341)	η^2	
[b]LEIDS (mean±SD)				
Hopelessness	6.8 ± 4.8	9.2 ± 5.2	< .001	
Acceptance	1.9 ± 2.2	2.0 ± 2.6	.002	
Aggression	5.0 ± 4.3	8.6 ± 5.1	.049	**
Control	6.4 ± 3.8	7.3 ± 4.1	< .001	
Risk aversion	10.6 ± 4.5	12.0 ± 4.6	.001	
Rumination	11.4 ± 4.7	13.5 ± 4.2	.002	
Total score	42.2 ± 17.5	52.7 ± 17.3	.004	

* .05 < p > .001

** p < .001

[‡] N = 751 (low-irritable. N = 382, high-irritable, N = 369)

[a] IDS-SR total score *minus* the score on the irritability item.

[b] Controlled for current symptoms (IDS-total minus item 6), gender and age

Physiological Variables

Cortisol Awakening Rise

Cortisol awakening response was used to investigate HPA-axis function (Wüst et al., 2000). During the baseline assessment, patients were instructed to collect four cortisol samples on a regular (working) day shortly after the interview. Samples were taken at awakening and at 30, 45, and 60 minutes after the first sample, after which they were returned by mail after collection. Median time between the interview and saliva sampling was 9.0 days (25^{th}–27^{th} percentile, 4–22 days). Outcome measures were the area under the curve with respect to the ground (AUCg) and the area under the curve with respect to the increase (AUCi) (Pruessner et al., 2003, Vreeburg et al., 2009a).

Cholesterol

Total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL), and cholesterol levels (both measures of serum cholesterol) were assayed from a blood sample taken after an overnight fast (Van Reedt Dortland et al., 2010).

Heart Rate Variability (HRV)

Heart rate variability (HRV) was assessed using a VU-AMS monitoring system (De Geus et al., 1995) which was worn during most of the baseline measurement (average registration 99.9 minutes). The various phases of the session (resting baseline, interviews, and a cognitive task) were marked using an event button. Mean heart rate, standard deviation of the interbeat intervals (SDNN), and the different measures of respiratory sinus arrhythmia (RSA) were calculated from the interbeat interval (IBI) time series and respiration signal (De Geus et al., 1995, Goedhart et al., 2007, Houtveen et al., 2002). For the current study, we investigated SDNN and RSA measured in (supine) rest condition (during which no interview was conducted) and during performance of a cognitive test (test condition) (Licht et al., 2008).

Data Screening

Data were checked for missings and outliers, normality of distributions, and homogeneity of variances. 145 of the 913 participants did not return their questionnaire package resulting in 145 missings on all variables of the LEIDS-R. On the age of onset variable, 162 participants had missing values. In about half of the other variables, a low number of missing values (<20) were replaced with the series mean of their subgroup (Irr+/Irr–) according to Tabachnik and Fidell (Tabachnik and Fidell, 2007). The dataset was complete for the other variables.

Table 2

Demographic and clinical characteristics of low and high irritable depressed patients multivariate results[a]

	Low-irritable (n = 323)	High-irritable (n = 301)	η^2	
Age of Onset (mean±SD)	29.0 ± 13.2	26.9 ± 12.4	.001	
Beck Anxiety Inventory (mean±SD)	16.6 ± 9.5	23.9 ± 11.3	.008	**
LEIDS (mean±SD)				
Aggression	5.0 ± 4.2	8.8 ± 5.1	.073	***
NEO FFI (mean±SD)				
Neuroticism	41.2 ± 6.8	45.3 ± 6.1	.006	*
Openness	31.1 ± 5.1	30.6 ± 5.9	< .001	
Agreeableness	44.0 ± 5.0	41.4 ± 5.6	.024	***

* .085 < p > .05

** .05 < p > .001

***p < .001

[a] Controlled for current symptoms (IDS-total minus item 6), gender and age.

Table 3

Psychophysiological measures

	Low-irritable (n = 294)	High-irritable (n = 218)	η^2
Cortisol (mean±SD)			
[a]AUCi	1.9 ± 4.9	2.1 ± 5.2	.001
[b]AUCg	18.1 ± 6.2	18.2 ± 5.8	< .001
	(n =487)	(n = 419)	
[c]Cholesterol (mean±SD)			
Total cholesterol	5.2 ± 1.1	5.1 ± 1.1	.001
LDL cholesterol	3.2 ± 1.0	3.2 ± 1.0	< .001
HDL cholesterol	1.6 ± 0.4	1.6 ± 0.4	.001
	(n = 470)	(n = 404)	
[d]Heart Rate Variability (mean±SD)			
RSA_{rest}	41.9 ± 27.7	45.6 ± 29.6	.002
RSA_{test}	40.8 ± 23.0	43.4 ± 23.9	.001
$SDNN_{rest}$	71.2 ± 30.9	73.3 ± 31.8	.001
$SDNN_{test}$	62.2 ± 23.1	63.9 ± 22.9	.002

[a] Controlled for sex, physical activity, cardiovascular disease, time of awakening and hours of sleep.

[b] Controlled for smoking, physical activity, cardiovascular disease, working on testing day, hours of daylight in month of testing.

[c] Controlled for current symptoms (IDS-total minus item 6), sex, age, smoking, alcohol abuse and dependence and antidepressant use.

[d] Controlled for current symptoms (IDS-total minus item 6), sex, age, smoking, alcohol abuse and dependence, antidepressant and heartmedication-use and heart disease.

After removal of outliers (scores higher or lower than 2 standard deviations from the mean) (Vreeburg et al., 2009a), cortisol data were normally distributed. There were no statistical outliers (based on Cook's distances and studentized residuals) on any of the other variables.

Statistical Analyses

Group differences (Irr+ versus Irr−) were investigated by general linear models (GLMs). This was done in two steps. First, data were explored by using separate univariate GLMs with group (Irr+/Irr−) as the between subjects factor. Alpha was set at 0.05, however all outcome variables significant at the $P < .15$ level in these univariate analyses were entered in a multivariate GLM to take into account correlations among the dependent variables. Covariates were included in the univariate and multivariate analyses in order to reduce error variance (Stevens, 2002). The choice of covariates in each of the analyses was based on literature review and results of previous studies conducted in NESDA (Penninx et al., 2008, Vreeburg et al., 2009b). Age, gender, and current depression symptoms were included as covariates in the GLMs for the LEIDS-R and NEO-FFI subscale and total scores. For the cortisol measures, we entered physical activity, smoking, cardiovascular disease, whether the participant was working on the day of data collection and hours of daylight in the month of data collection as covariates. In the HRV and cholesterol analyses, covariates were age, gender, depression severity, alcohol dependence and abuse, use of antidepressants, and heart medication. Participants were classified as nonsmoker, former smoker, smoker, or heavy smoker (>20 tobacco consumptions a day), and similar categories were made for alcohol use: nondrinker, mild drinker (<7 units/week), moderate drinker (7–14 u/wk), and heavy drinker (≥15 u/wk). Energy spent on physical activity per week was measured with the International Physical Activity Questionnaire (Booth, 2000). Chi-square statistics were used in case of categorical variables. Logistic regression analysis was used to control for potential confounders in relationships involving categorical variables.

Results

Demographic and Clinical Characteristics

Univariate analyses showed that the irritable depressed group was significantly older than the non-irritable depressed group ($F(1, 911) = 10.7$; $P = .001$). There was no significant difference in the distribution of males and females over the two groups ($\chi^2(1) = .004$; $P = .95$). Participants in the Irr+ group had been recruited from specialized mental health institutions more often than participants in the Irr− group ($\chi^2(2) = 16.4$; $P < .001$). Table 1. shows that the Irr+ group also had notably higher scores on severity of depression (IDS total minus Item 6; Irritability) ($F(1, 911) = 232.9$; $P < .001$) than the Irr− group. This pattern was present at each recruitment site, with 9 points difference between Irr+ and Irr− in primary care ($F(1, 367) =$

76.6; P < .001) and specialized mental health care (F(1, 466) = 102.3; P < .001) and 13 points difference in the general population (F (1, 72) = 47.5; P < .001). Irr+ participants also had higher anxiety (BAI total) symptoms (F(1, 911) = 134.2; P < .001) and more lifetime anxiety disorders ($\chi^2(1) = 5.5$; P = .019). Current GAD ($\chi^2(1) = 14.7$; P < .001), panic disorder ($\chi^2(1) = 22.8$; P < .001), and social anxiety disorder ($\chi^2(1) = 17.3$; P < .001) were also more prevalent in the Irr+ group. More patients in the Irr+ group had previously attempted suicide than patients in the Irr− group (25% versus 17%; $\chi^2(1) = 8.3$; P = .004). However, an additional logistic regression analysis showed that the association between irritability and suicidality was no longer statistically significant after controlling for depression severity. Patients in the Irr+ group scored higher on three mania items of the MDQ: talkativeness ($\chi^2(1) = 4.03$; P = .045), racing thoughts ($\chi^2(1) = 10.47$; P = .001), and distractibility ($\chi^2(1) = 14.57$; P < .001).

Cognitive Vulnerability

The Irr+ group scored higher on all subscales of the LEIDS-R, with exception of the acceptance subscale. The Irr+ group also had a significantly higher LEIDS-R total score ($F(1, 766) = 68.8$; $P < .001$). After adding age, gender, and IDS total score as covariates, only the difference between the scores on the aggression subscale of the LEIDS-R remained significant ($F(1, 763) = 39.4$; $P < .001$).

Personality

The Irr+ group had significantly higher neuroticism scores ($F(1, 908) = 116.06$;$P < .001$) and scored significantly lower on extraversion ($F(1, 908) = 39.48$; $P < .001$), openness ($F(1, 909) = 6.71$; $P = .010$), agreeableness ($F(1, 908) = 48.58$; $P < .001$), and conscientiousness ($F(1, 908) = 5.38$; $P = .021$) than the Irr- group. After correcting for age, gender, and total IDS score, the differences on neuroticism and agreeableness remained statistically significant.

Multivariate Analyses

The multivariate analyses (shown in Table 2.) yielded similar results, with significant differences between Irr+ and Irr− on BAI total score ($F(1, 619) = 4.84$; $P = .028$), LEIDS-R aggression ($F(1, 619) = 48.40$; $P < .001$), and agreeableness ($F(1, 619) = 14.96$; $P < .001$). Neuroticism was significant at trend level ($F(1, 619) = 3.71$; $P = .055$)

Physiological Variables

Table 3. shows the outcomes on the (psycho)physiological markers. There were no significant differences in cortisol awakening response (CAR) between the Irr− and Irr+ irritable group. HDL cholesterol was significantly higher in the Irr− group ($F(1, 911) = 5.69$; $P = .017$), but this difference was no longer significant after entering the covariates gender, age, smoking, alcohol abuse and dependence, and antidepressant and heart-medication use. Both groups did not differ significantly on measures of HRV either (all P values > .12), with and without correction.

Depressed patients who were irritable both at baseline and at one-year follow-up (Irr++) (N = 138) differed from depressed patients who were non-irritable on both baseline and one-year follow-up (Irr−−) (N = 202) on largely the same outcomes. Fewer patients in the Irr++ group were recruited from primary health care or the community ($\chi^2(1) = 5.67$; P = .020), and they scored higher on comorbid anxiety disorders. Their depression severity (IDS minus irritability) was also higher (F(1, 338) = 77.74; P < .001). They scored higher on aggression reactivity (F(1, 319) = 36.35; P < .001) and total LEIDS-R score (F(1, 319) = 3.94; P = .048), after correction for depression severity, age, and gender. Irr++ participants also had higher neuroticism (F(1, 335) = 12.94; P < .001) and lower agreeableness (F(1, 335) = 8.62; P = .004) scores, after correction for age, gender, and depression severity. No physiological differences were found between the Irr++ and Irr−− groups.

Discussion

The present study showed that approximately half of the patients with a primary diagnosis of unipolar depression also have high levels of irritability. This is consistent with earlier research (Fava et al., 2009, Perlis et al., 2009). Other studies have shown that the prevalence of anger attacks in patients with unipolar depression is only slightly lower at approximately 40% (Fava and Rosenbaum, 1998, Fava et al., 1991, Fava et al., 1993). These studies, however, concerned patients recruited from secondary care facilities. In the current study, almost 60% of the patients recruited from psychiatric outpatient departments were classified as irritable. Irritability has been defined as "a feeling characterized by reduced control of temper" which often results in verbal or behavioral aggression (Snaith and Taylor, 1985). Although irritability should be distinguished from more violent forms of aggressive and assaultive behavior, milder and more severe forms of irritability (e.g., anger attacks) may lie on a continuum (Snaith and Taylor, 1985). Future research may investigate the exact relationship between irritability during depression and its outward manifestations such as anger attacks.

Clinical Characteristics of Irritable versus non-Irritable Depression

Irritable depressed patients were more severely depressed than non-irritable depressed patients. The difference in IDS scores was 10 points, which is more than one standard deviation. The severity of anxiety symptoms and suicidality was also higher. Moreover, irritable depressed patients were more often diagnosed with a comorbid anxiety disorder. The onset of depression was approximately two years earlier in the irritable depressed. They were also somewhat older at study entry and were more often recruited from secondary care facilities. With regards to their psychological profile, differences between irritable and non-

irritable depressed patients were observed on a broad range of personality traits and cognitive vulnerability indices. However, after correction for depression severity, irritable depressed patients only had higher scores of aggression reactivity and lower scores of the personality trait agreeableness. Although participants are categorized into high- and low-irritable groups on the basis of one symptom, the psychological profile observed in the present study supports the validity of the subgroups.

Physiological Differences between Irritable and non-Irritable Depression

We found no differences between irritable and non-irritable depressed patients on any of the physiological markers that were investigated. Although HDL cholesterol was significantly higher in non-irritable patients, this result was no longer significant after correction for several covariates. No differences were observed on measures of heart rate variability (HRV) and cortisol awakening rise (CAR). We subsequently investigated the possibility that these physiological markers are related to more stringently defined subtypes, by selecting participants who were also depressed at one-year follow-up and showed either high or low scores of irritability at both time points. This comparison produced exactly the same pattern of findings. Irritable depressed patients had a greater prevalence of anxiety disorders and higher depression severity and aggression reactivity. Again, no differences were found on any of the physiological measures after correction for overall depression severity. The absence of differences at the physiological level was unexpected since studies in healthy samples have found greater HPA-axis reactivity (Bohnke et al., 2010, Gerra et al., 1997) and increased cardiac reactivity as a function of hostility and aggression (Neumann et al., 2004, Virtanen et al., 2003). However, in a population-based sample anxiety and hostility were not related with HRV but with baroreflex sensitivity, which may be a more sensitive measure of vagal activity (Virtanen et al., 2003). In depressed patients, the studies that investigated cardiac and HPA-axis reactivity concern comparisons between patients with and without anger attacks. These studies found higher cholesterol concentrations in depressed patients with anger attacks (Fava et al., 1996). We found no support for this finding in the present sample of irritable versus non-irritable depressed patients.

In the present study, HRV was assessed at rest and during a task that required cognitive effort. Cortisol samples were collected at home. It has been suggested that depressed patients with anxiety-aggression behaviors also have a greater sensitivity to stress (Van Praag, 1996b). It could be that irritable depressed patients only show greater HPA-axis and cardiac reactivity when exposed to a more significant stressor than performing a cognitive test. This could be further tested using the same measures as in the present study in combination with laboratory stress or anger induction paradigms. The clinical and psychological characteristics observed in the irritable depressed patients resemble a subtype of depression proposed by Van Praag (Van Praag, 1994, 1996b, 2001). He stated that aggression combined with anxiety is the primary

feature of a subtype of depression which he called "stressorprecipitated, cortisol-induced, serotonin-related, anxiety/aggression- driven" (SeCA) depression (Van Praag, 1996a). This subtype may be further characterized by increased 5-HT disturbances, in which low mood is a secondary symptom (Van Praag, 1994) and with aggression disturbances as primary symptom. Unfortunately, markers of 5-HT function were not available in the present study.

Symptoms of Bipolar Disorder in Irritable versus non-Irritable Depression

We also observed differences between irritable and non-irritable depressed patients on three symptoms of hypomania as measured by the MDQ: distractibility, talkativeness, and racing thoughts. Future longitudinal analyses of NESDA participants may show whether irritability during depression is a risk factor for the development of bipolar disorder.

Strengths and Limitations of the Current Study

The current study had several strengths, including a rather large sample size of currently depressed patients. Diagnoses were determined using a standardized interview. Patients were recruited from different sites and facilities, which increases the generalizability of the findings. The cross-sectional design is a limitation. This was partially remediated by the inclusion of a one-year follow-up measurement of the clinical variables, which allowed us to investigate a more stable subgroup of irritable depressed patients. Although other studies used the same method (Fava et al., 2009, Perlis et al., 2009), the fact that the distinction between irritable and non-irritable depressed was based on just one symptom can be seen as a limitation. We interpret the selective differences on cognitive reactivity and personality as supporting the validity of the distinction.

Future Directions

Our findings indicate several clinical differences between depressed patients with and without irritability. High levels of irritability during depression are associated with more severe depression, higher levels of anxiety, and more comorbid anxiety disorders. Anxiety during depression is associated with poorer outcome, including higher risk of chronic depression, poorer treatment response (Van Valkenburg et al., 1984), and increased suicide incidence (Fawcett and Kravitz, 1983). Moreover, we found higher levels of aggression reactivity, hopelessness, and disagreeableness in irritable depressed patients. Both hopelessness and aggression reactivity have been associated with increased suicide risk (Antypa et al., 2009). Therefore, it is important to continue the investigation into possible underlying mechanisms of this form of depression. There is evidence that depressed patients with aggression

dysregulation problems have more pronounced 5-HT alterations (Cleare and Bond, 2000, Lopez-Ibor et al., 1985, Van Praag, 1994, 1996b, Young et al., 2007). Moreover, there is some evidence that depression in combination with aggression (hostility, anger) is partly under genetic control (Gonda et al., 2011).

Conclusion

In this cross-sectional assessment, approximately half of depressed patients were classified as irritable. These patients differ from low-irritable depressed patients on several other aspects of the clinical presentation, including depression severity and comorbid anxiety. Personality and cognitive vulnerability measures also differ between these groups. Future longitudinal studies in depressed patients are needed to investigate the consequences of high levels of irritability in terms of risk of bipolar disorder, course of disease and treatment response.

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Chapter 3
The effects of MAOA genotype, childhood trauma, and sex on trait and state-dependent aggression

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Abstract

Monoamine oxidase A (MAOA) genotypic variation has been associated with variation in aggression, especially in interaction with childhood trauma or other early adverse events. Male carriers of the low-expressing variant (MAOA-L) with childhood trauma or other early adverse events seem to be more aggressive, whereas female carriers with the high-expressing variant (MAOA-H) with childhood trauma or other early adverse events may be more aggressive. We further investigated the effects of MAOA genotype and its interaction with sex and childhood trauma or other early adverse events on aggression in a young adult sample. We hypothesized that the association between genotype, childhood trauma, and aggression would be different for men and women. We also explored whether this association is different for dispositional (trait) aggression versus aggression in the context of dysphoric mood. In all, 432 Western European students (332 women, 100 men; mean age 20.2) were genotyped for the MAOA gene. They completed measures of childhood trauma, state and trait measures of aggression-related behaviors (STAXI), and cognitive reactivity to sad mood (LEIDS-R), including aggression reactivity. Women with the MAOA-H had higher aggression reactivity scores than women with the MAOA-L. This effect was not observed in men, although the nonsignificant findings in men may be a result of low power. Effects on the STAXI were not observed, nor were there gene by environment interactions on any of the aggression measures. A protective effect of the low-expression variant in women on aggression reactivity is consistent with previous observations in adolescent girls. In females, the MAOA-H may predispose to aggression-related problems during sad mood.

Introduction

Monoamine oxidase A (MAOA) is an enzyme essential for the degradation of monoamines in the central nervous system (Oreland, 1991). Previous research has shown that MAOA plays a major role in aggression. In one of the first studies, a point-mutation in the gene that codes for MAOA, causing complete MAOA deficiency, was associated with criminal and violent behaviors in males. This effect was seen over multiple generations in the family studied (Brunner et al., 1993). This link between lower MAOA enzyme activity and aggression has been confirmed in studies using animal models (Cases et al., 1995) and in human studies that used positron emission tomography to measure MAOA function in vivo (Alia-Klein et al., 2008, Soliman et al., 2011). The MAOA gene is located on the X chromosome (Xp11.23-11.4) and has a variable number of tandem repeats (VNTR). Alleles with 3.5 or 4 copies lead to 2–10 times more efficient transcriptional activity (indicating high expression; MAOA-H) than alleles with three copies (low expression; MAOA-L) (Sabo et al., 1998). An early study showed that maltreated boys with the MAOA-L genotype were at greater risk to develop antisocial problems than maltreated boys with the MAOA-H genotype (Caspi et al., 2002). This finding has been replicated (Cicchetti et al., 2010, Ducci et al., 2008, Enoch et al., 2010, Foley et al., 2004, Huang et al., 2004, Kim-Cohen et al., 2006, Nilsson et al., 2006) but not consistently (Alia-Klein et al., 2008, Young et al., 2006). Although most studies have shown that the MAOA-H variant is associated with less aggressive behavior in males, this variant may be a risk factor for increased aggressive behaviors in adolescent girls who experience early psychosocial risk factors (Åslund et al., 2011, Sjoberg et al., 2007). Problems in aggression regulation are a common symptom of many psychiatric disorders. For instance, up to 30–40% of depressed patients seem to experience some form of aggression regulation problems during their depression, ranging from irritability (Perlis et al., 2009, Verhoeven et al., 2011) to anger attacks (Fava and Rosenbaum 1999, Van Praag, 2001). Consistent with this, MAOA has been linked to both aggression and the development and pharmacological treatment of depression (Aklillu et al., 2009, Pare, 1985). This may suggest that the relationship between MAOA and aggression depends on the context of aggression. Indeed, a previous study has shown that the effects of the MAOA gene on aggression are most prominent in an aggression-provoking situation (Mcdermott et al., 2009). It is therefore of interest to assess the role of the MAOA gene in aggression-related behaviors in the context of sad mood. In this study, we investigated the effects of MAOA genotype and its interaction with sex and early adversity on different aspects of aggression in young adults, that is, state aggression but also aggression in the context of depression. We hypothesized that the association between genotype and childhood trauma would be different for men and women. Specifically, we expected that male carriers of the low-expression MAOA variant would express higher levels of aggression-related behaviors than carriers of the high-expression variant, in particular in the context of early adversity. We expected an opposite pattern in females.

Methods

Participants

A total of 432 participants aged between 17 and 39 participated in the study (332 women, 100 men). Participants were recruited via advertisements, flyers, and posters in the university buildings (University of Leiden, the Netherlands). Participants had to be of Western European descent (i.e., all four grandparents born in the Netherlands, Germany, France, Belgium, Luxemburg, Austria, Switzerland, Ireland, the United Kingdom, or Scandinavia). Those suffering from a current depressive episode were excluded from the analyses. The presence of more women than men in the current sample is useful because, unlike men, women can be either hetero- or homozygous for the MAOA genotype.

Measures

Childhood trauma was measured using the 28-item version Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1997, Thombs et al., 2009). This self-report questionnaire has been validated both in clinical and in nonclinical samples. The CTQ has five subscales (Emotional abuse, Physical abuse, Sexual abuse, Emotional neglect, and Physical neglect) and each item is rated on a Likert scale ranging from 1 (never true) to 5 (very often true). We divided participants in two groups: those who reported none/minimal-to-moderate levels of childhood trauma and those who reported moderate-to-severe levels of childhood trauma. The distinction was based on severity norm scores from a sample of North American college students (Bernstein, D. P. et al., 1997), with participants scoring lower than the cutoff score of 38 assigned to the none/ minimal-to-moderate levels of childhood trauma group and those scoring over 38 assigned to the moderate-to severe levels of childhood trauma group. The Spielberger State-Trait Anger Expression Inventory (STAXI) (Forgays et al., 1997, Spielberger et al., 1983, Van Der Ploeg et al., 1982) was used to measure aggression- related behaviors both as an emotional state and as a personality trait. Both versions of the STAXI consist of 10 items with a 4-point Likert scale. Cognitive reactivity was measured with the Leiden Index of Depression Sensitivity – Revised (LEIDS-R) (Van Der Does, 2002, 2005, Williams, 2008). This 34- item self-report questionnaire has six subscales (Aggression Reactivity [AGG], Hopelessness/ Suicidality Reactivity [HOP], Acceptance/Coping [ACC], Control/Perfectionism [CTL], Risk Aversion [RAV], and Rumination on Sadness [RUM]). It instructs participants to indicate how their thinking patterns change when they experience mild dysphoria. Questions are answered on a 0–4 Likert scale. The AGG and HOP subscales and the LEIDS-R total score were the primary outcome measures for this study. The AGG and HOP reactivity subscales have been found to be strongly associated with irritability in depressed patients (Verhoeven et al., 2011) and with suicidality (Antypa and Van Der Does, 2010, Verhoeven et al., 2011).

Table 1

Sample characteristics women (N = 332)

	LL genotype (N = 37)	HL genotype (N = 156)	HH genotype (N = 139)	F	df	p
Age (mean±SD)	19.6±1.8	20.1±3.01	20.0±2.4	.534	2	.59
STAXI Trait total score (mean±SD)	16.3±3.6	15.8±3.7	17.1±4.6	3.760	2	.02
STAXI State total score (mean±SD)	15.11±3.8	14.5±3.1	14.9±3.5	.581	2	.56
LEIDS-R total score (mean±SD)	37.6±13.3	40.2±15.7	42.1±14.6	1.481	2	.01
LEIDS-R HOP (mean±SD)	4.3±3.0	5.3±4.0	5.1±3.9	.967	2	.38
LEIDS-R ACC (mean±SD)	1.8±2.3	1.5±1.8	1.5±1.8	.400	2	.67
LEIDS-R AGG (mean±SD)	5.8±3.4	6.4±4.4	7.1±4.3	1.852	2	.16
LEIDS-R CTL (mean±SD)	7.6±3.2	7.6±3.9	7.7±3.4	.044	2	.96
LEIDS-R RAV (mean±SD)	8.6±3.8	9.1±3.9	9.7±3.8	1.729	2	.18
LEIDS-R RUM (mean±SD)	9.6±3.7	10.5±4.1	11.0±4.0	1.990	2	.14
Past depression (MDQ) (%yes)	29.7	39.7	32.4	2.357	2	.31
Abuse (% moderate to severe on CTQ)	16.2	13.5	20.1	2.378	2	.30

STAXI: Spielberger State Trait Anger Expression Inventory

LEIDS-R: Leiden Index of Depression Sensitivity – Revised

HOP: Hopelessness

ACC: AcceptanceAGG: Aggression

CTL: Control

RAV: Risk Aversion

RUM: Rumination

MDQ: Mood Disorder Questionnaire

CTQ: Childhood Trauma Questionnaire

Table 2

Sample characteristics men (N = 100)

	L genotype (N = 35)	H genotype (N = 65)	F	df	p
Age (mean±SD)	20.6±2.3	20.7±3.1	.003	1	.96
STAXI Trait total score (mean±SD)	15.1±4.2	15.4±3.3	.114	1	.74
STAXI State total score (mean±SD)	13.6±2.5	14.4±3.0	1.675	1	.20
LEIDS-R total score (mean±SD)	44.3±15.5	38.1±16.4	3.350	1	.07
LEIDS-R HOP (mean±SD)	5.2±3.8	4.5±3.8	.733	1	.40
LEIDS-R ACC (mean±SD)	3.0±2.3	2.5±2.8	.824	1	.37
LEIDS-R AGG (mean±SD)	7.7±4.8	6.5±4.1	1.733	1	.19
LEIDS-R CTL (mean±SD)	7.3±4.0	6.7±3.5	.745	1	.39
LEIDS-R RAV (mean±SD)	9.4±4.1	7.9±4.0	3.140	1	.08
LEIDS-R RUM (mean±SD)	11.7±4.7	10.1±4.8	2.721	1	.10
Past depression (MDQ) (%yes)	28.6	26.2	.067	1	.76
Abuse (% moderate to severe on CTQ)	22.9	13.8	1.309	1	.25

STAXI: Spielberger State Trait Anger Expression Inventory

LEIDS-R: Leiden Index of Depression Sensitivity – Revised

HOP: Hopelessness

ACC: AcceptanceAGG: Aggression

CTL: Control

RAV: Risk Aversion

RUM: Rumination

MDQ: Mood Disorder Questionnaire

CTQ: Childhood Trauma Questionnaire

The LEIDS-R total score is associated with serotonin vulnerability (response to tryptophan depletion) (Booij and Van Der Does, 2007) and with the interaction of serotonin transporter gene polymorphism and early-life events (Antypa and Van Der Does, 2010).

Procedure

All measures were obtained in a single session. All participants signed informed consent prior to participation and either received €10 or study credits. The research was approved by the Ethics Committee of the Institute of Psychology of Leiden University. Saliva samples were collected using Oragene Self- Collection Kits – DISC format (DNA Genotek Inc, Ottawa, Ontario, Canada); 200 lL of saliva was kept in lysis buffer (100 mmol/L NaCl, 10 mmol/L EDTA, 10 mmol/L Tris pH 8, 0.1 mg/mL proteinase K, and 0.5% w/v sodium dodecyl sulfate) until further processing. DNA isolation Genomic DNA was isolated from the samples using the Chemagic kit on a Chemagen Module I workstation (Chemagen Biopolymer-Technologie AG, Baesweiler, Germany). DNA concentrations were quantified by OD260 measurement and by agarose gel electrophoresis. The average yield was approximately 4 lg of genomic DNA per sample.

Polymerase chain reaction amplification

The region of interest from the MAOA gene was amplified by triplex polymerase chain reaction (PCR) using the following primers: a 6-carboxyfluorescein-labeled Medium Resolution (MR) primer (5'-GGATAACAATT TCACACAGG-3'), forward primer (5'-ggataacaatttcacacagg ACAGCCTGACCGTGGAGAAG-3'), and a reverse primer (5'-GGACCTGGGCAGTTGTGC-3'). Typical PCR reactions contained between 10 and 100 ng genomic DNA template, 1 pmol of forward primer, and 10 pmol of labeled MR and reverse primers. PCR was carried out in the presence of 5% dimethyl sulfoxide with 0.3 U of BioThermAB polymerase (GeneCraft, Munster, Germany) in a total volume of 30 lL using the following cycling conditions: initial denaturation step of 5 min at 94°C, followed by 38 cycles of 30 sec 94°C, 30 sec 55°C, 30 sec 72°C, and a final extension step of 4 min 72°C.

Analysis of PCR products

One microliter of PCR product was mixed with LIZ-500 size standard and formamide and run on an AB 3100 genetic analyzer setup for genotyping with 50-cm capillaries. Results were analyzed using Genescan software version 3.7 (Applied Biosystems, Carlsbad, California) and alleles were scored visually.

Statistical analyses

Following screening for accuracy of data entry and verification of statistical assumptions, chi-square statistics and generalized linear model (GLM) were used to investigate differences in demographic and trauma frequency between the genotypes. Next, the influence of genotype and its interactions with childhood trauma and sex were analyzed in two steps. First, we included both men and women in the analyses, but excluded the heterozygotes (resulting in N = 276). In case of a significant sex by genotype interaction, a second set of analyses in female participants only was performed, including both homo- (HH and LL) and heterozygote (HL) females. Since MAOA genotype is X-linked, we chose to exclude men in this set of analyses to ensure we would only be looking at the effect of genotype without the effect of sex, while still obtaining sufficient power. Data were analyzed using GLM for (M)ANOVA, including MAOA genotype, childhood trauma, and (when relevant) sex as a between-subject factor. In case of threegroup comparisons Tukey's test was used. IBM SPSS 19 (IBM Corporation, Armonk, New York) was used for data analysis.

Results

Preliminary analyses

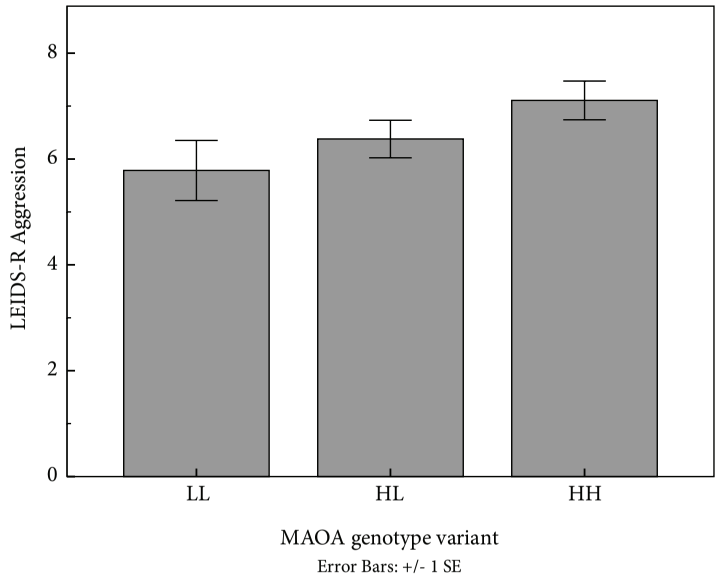
Genotype frequencies were as follows for men: L, 35%; H, 65%; and for women: LL, 11.10%; LH, 47%; HH, 41.90%. As the MAOA-LPR polymorphism is X-linked, the Hardy–Weinberg equilibrium can only be reported for women for whom frequencies were in the equilibrium ($\chi^2(1) = 0.47$; $P > 0.05$). As data obtained on both STAXI scales were rightskewed, square root transformed values were used.

Combined male/female sample (MAOA-H/HH vs. MAOA-L/LL)

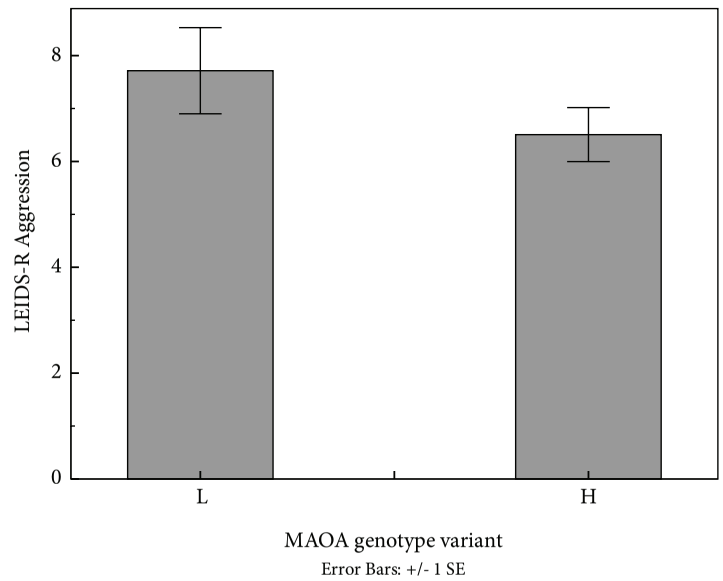
Sample characteristics and mean scores on the behavioral measures, as a function of MAOA genotype, are presented in Tables 1. (women) and 2. (men).

Demographics

The group of high-allele carriers (MAOA-H/HH) comprises significantly more women than the low-allele (MAOA-L/LL) group ($\chi^2(1) = 10.23$; $P \leq 0.01$). The groups did not differ in age.



(A) Women



(B) Men

Figure 1

Leiden Index of Depression Sensitivity-Revised (LEIDS-R) Aggression-scores as a function of sex and genotype; figure (A) represents women, figure (B) represents men. Data represent mean-scores ± SE

STAXI

Main effects

No effect of genotype was observed on the STAXI scales. Women scored approximately 2 points higher than men on the STAXI Trait ($F(1, 268) = 5.36$; $P = 0.02$, partial $\eta^2 = 0.02$) and 1 point on the STAXI State ($F(1, 268) = 5.24$; $P = 0.02$, partial $\eta^2 = 0.02$).

Interaction effects

No significant interaction effect of genotype with childhood trauma and/or sex on STAXI scores was found.

LEIDS-R

Main effects

Only on the LEIDS-R HOP scale did we find a main effect. Those who had experienced moderate-to-severe levels of childhood trauma scored significantly higher ($F(1, 268) = 4.90$; $P = 0.03$, partial $\eta^2 = 0.02$) on HOP reactivity. Main effects of MAOA genotype and sex were not significant for this scale.

Interaction effects

An interaction effect of MAOA genotype by sex was found for the AGG reactivity scale ($F(1, 268) = 5.48$; $P = 0.02$, partial $\eta^2 = 0.02$) (Figure 1.). The secondary analyses for men and women separately revealed that women with the high-expression variant had higher scores on this subscale compared with women with the low-expression variant ($F(1, 172) = 5.02$, $P = 0.03$, partial $\eta^2 = 0.03$). No differences were observed in men, nor were there any interactions with childhood trauma. For the LEIDS-R total score, we found a significant interaction effect between MAOA genotype and sex ($F(1, 268) = 7.90$; $P = 0.01$, partial $\eta^2 = 0.03$). A rerun of the analysis for men and women separately showed that MAOA-HH women had higher LEIDS-R total scores than MAOA-LL women ($F(1, 172) = 7.06$, $P = 0.01$, partial $\eta^2 = 0.04$), while no differences were observed in men. This post hoc analysis for women separately also revealed a significant interaction between genotype and childhood trauma ($F(1, 172) = 4.70$, $P = 0.03$, partial $\eta^2 = 0.03$). Within the group of women reporting childhood trauma, the HH carriers had higher LEIDS-R total scores compared with the LL carriers ($F(1, 32) = 8.42$, $P = 0.01$, partial $\eta^2 = 0.21$). This effect was absent in women without a history of childhood trauma or men.

Analyses of the secondary outcome measures on the LEIDS-R showed gene by sex interactions on both RUM ($F(1, 268) = 5.43$, $P = 0.02$, partial $\eta^2 = 0.02$) and RAV ($F(1, 27) = 10.03$, $P \leq 0.01$, partial $\eta^2 = 0.04$) reactivity. MAOA-HH women scored higher than MAOA-LL women on the RUM subscale. A rerun of the analyses for men and women separately showed that women with the high-expression variant scored significantly higher than those with the low-expression variant on RUM ($F(1, 172) = 6.43$, $P = 0.01$, partial $\eta^2 = 0.04$) as well as RAV ($F(1, 172) = 4.25$, $P = 0.04$, partial $\eta^2 = 0.02$), whereas in men no such difference was seen. A three-way interaction effect of MAOA genotype by sex by childhood trauma was detected for the RAV subscale ($F(1, 268) = 4.67$, $P = 0.03$, partial $\eta^2 = 0.02$). A subsequent analysis for men and women with and without childhood trauma history showed that MAOA-HH women with a history of childhood trauma had higher risk aversion scores than MAOA-LL women with a history of childhood trauma ($F(1, 32) = 5.80$, $P = 0.02$, partial $\eta^2 = 0.15$). Such effects were not observed for women without childhood trauma, neither were any main or interaction effects observed in men only.

MAOA genotype in women

Given the sex by genotype interactions on the LEIDS-R AGG reactivity scale, total score as well as the RUM and RAV scale, a separate analysis in women was conducted including the heterozygotes to study these interaction effects in detail.

Main effects

We found a significant main effect of MAOA genotype for the LEIDS-R total score ($F(1, 326) = 3.17$; $P = 0.04$, partial $\eta^2 = 0.02$) and visual inspection suggested a dose–effect relationship. Subsequent post hoc Tukey's tests did not reveal significant group differences between the HH, HL, and LL group, but women with the HH genotype tended to have higher LEIDS-R total scores than women with the LL genotype ($P = 0.099$). An analysis at the allele level (LL, HL vs. HH) showed a trend toward greater aggression reactivity scores in women who were homozygous for the H allele compared with those with one or two L alleles ($F(1, 328) = 3.40$, $P = 0.07$, partial $\eta^2 = 0.010$). Such effects were not observed on the other primary outcome measures. Analyses of the secondary outcome measures showed a significant difference between genotypes on the RAV reactivity subscale ($F(1, 326) = 3.20$; $P = 0.04$, partial $\eta^2 = 0.01$), although the post hoc group comparisons were not significant. No other effects of genotype were found.

Interaction effects

No interaction effects were found.

Discussion

The aim of this study was to investigate the role of the MAOA gene and its interaction with childhood trauma and sex on measures of trait and state-dependent aggression- related behaviors in a healthy young adult sample. We found that women with the MAOA-HH genotype scored higher on some measures of aggression compared with MAOA-LL women. Specifically, MAOA-HH women reported more aggressive thoughts and behavior in relation to sad mood (LEIDS-R AGG scale) compared with MAOA-LL women. Such effects on the LEIDS-R AGG scale did not occur in men, nor did we see any effects on more general trait and state measures of aggressive behaviors such as the STAXI. This discrepancy between the results on the LEIDS-R and the STAXI may be explained by the fact that the STAXI contains two separate scales for state and for trait, whereas the LEIDS-R measures aggression in the context of dysphoria. The notion that the effects of MAOA genotype may be context dependent is consistent with an experimental study in healthy males (Mcdermott, R. et al., 2009). Using an aggression provocation task, it was found that the impact of the MAOA-L variant on aggressive behavior in males was largest in the context of aggression provocation (Mcdermott, R. et al., 2009). The presently found sex-specific effects and their direction are in line with Sjöberg et al. (2007), who reported more criminal behavior in MAOA-HH adolescent girls with higher psychosocial risk compared with adolescent girls without this risk. Our study is a first in showing an association between the high-expression MAOA variant and aggression-related behaviors in adult women. Sjöberg et al. found only effects in girls with higher levels of psychosocial adversity, whereas in our sample, the effects were irrespective of childhood trauma history. Differences in the type of childhood trauma measured (Sjöberg: multifamily housing and sexual abuse; current study: emotional and physical neglect and abuse, sexual abuse) may account for the discrepancies in findings between the studies. We also found sex-specific effects of the MAOA-H variant on total LEIDS-R score, RAV and RUM. RUM is known to predict higher levels of depressive symptoms, recurrence of depressive episodes, as well as chronicity (Nolen-Hoeksema, 1991, Robinson and Alloy, 2003). Antypa et al. (2010) found higher scores on the LEIDS-R total score as well as on the RUM scale in healthy individuals who are carriers of the s allele of the serotonin transporter promoter polymorphism, a genotype commonly associated with depression (Du et al., 1999, Kaufman et al., 2006). We observed one significant three-way interaction of sex, genotype, and childhood trauma on the LEIDS-R RAV scale. Specifically, an association between risk aversion scores and the high MAOA expression variant was found only in women with a history of childhood trauma. The RAV scale measures the tendency to avoid not only risk but also interpersonal conflict and is the opposite of aggression. As the HH variant of the MAOA genotype is associated with increased aggression, we may speculate that the observed association between the MAOA-HH variant and risk aversion suggests that in the context of an early adversity, increased risk aversion behavior in HH homozygotes may be a compensatory mechanism for increased feelings of aggression. Another explanation of increased aggression in combination

with increased risk aversion in the context of early adversity is that MAOA-HH girls who show more aggression during early childhood may have experienced increased punishment for their aggression by their parents or caretakers, thus learning to avoid certain behaviors to avoid punishment or abuse. However, we did not have sufficient information to test for possible mechanisms accounting for these effects. Individuals who had experienced trauma in childhood had higher HOP reactivity scores than individuals without any history of childhood trauma, irrespective of sex or genotype. Interestingly, HOP reactivity has been found to be a predictor of risk for suicidal ideation or attempt in formerly and currently depressed samples (Antypa and Van Der Does, 2010, Williams et al., 2008). In addition, childhood trauma has been shown to be a predictor of suicidality (Agerbo et al., 2002, Beautrais et al., 1996, Bernet and Stein, 1999, Brent et al., 2002, Dube et al., 2001, Heim and Nemeroff, 2001, Johnson et al., 1999). Since our sample comprises healthy individuals, this study extends these observations, suggesting that childhood trauma may set the stage for tendencies toward thoughts of hopelessness. This might in turn lead to suicidal ideation, especially in the context of further genetic susceptibility or further stressors. The current study has some limitations, one of them being the relatively small number of men in the sample. Therefore, we cannot rule out the possibility that the lack of effects in men is due to a type II error. Indeed, Williams et al. (2009) found in a healthy sample that MAOA-L men had higher antisocial trait scores than men with the MAOA-H genotype, while no such difference was found in women. Notably, the majority of Williams' et al. sample consisted of men (67%). In interpreting our results, we should thus consider the possibility that the lack of results in men in the current sample may be due to its smaller size. Furthermore, we did not correct for multiple testing. Hence, the risk of false-positive observations cannot be ruled out. However, our study had the a priori aim to compare different types of aggression measures and their relationship to the MAOA genotype. Another limitation is that our aggression measures were all based on self-report. It would be of interest to extend this study using other measures of aggression such as observational measures, diary techniques, or laboratory aggression-induction procedures. A strength of this study is that we recruited a sample that was relatively homogeneous in terms of age, education, and ethnicity. Furthermore, participants were screened for mental health problems before enrolling in the study. However, a disadvantage of our recruitment strategy is that university students are likely to score relatively low on violence and aggression compared with the general population. Although mean scores on the STAXI (both State and Trait) did not differ much from norm scores for this questionnaire, it would be of interest for future studies to use the same methods and procedures in a community sample. To summarize, this study showed that some of the associations between aggression, genes, and diagnosis previously observed in non-adult patient samples can be generalized to healthy young adult samples. This is reflected by elevated scores on assessments measuring the tendency to display aggressive behaviors/thoughts in a context of sad mood, rather than in behavior or disease pattern itself.

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Chapter 4
Acute tryptophan depletion in remitted depressed patients with and without anger regulation problems: effects on symptoms, cortisol and testosterone

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Paper in preparation

Abstract

Introduction: Symptoms of anger and aggression occur in approximately 50% of patients with major depressive disorder. Both depression and aggression–related symptoms have been associated with serotonergic alterations. The current study tested the hypothesis that remitted depressed patients with anger regulation problems during their depression (MDD+A) are more sensitive to serotonin reductions than remitted depressed patients without anger regulation problems (MDD-A), reflected in greater mood and endocrine responses to acute tryptophan depletion (ATD).

Methods: 10 MDD+A and 16 MDD-A participants received a 102.5-g (high-dose ATD) and a 25.7-g (low-dose ATD) amino acid mixture in a counterbalanced, randomized, double-blind crossover design. Mood and anger-related symptoms were measured before and after intake of the amino acid mixture as were cortisol and testosterone.

Results: High-dose but not low-dose ATD transiently increased depressive symptoms and decreased testosterone levels, 7 hours after ATD. Mood-responses to high-dose ATD were more pronounced in the MDD+A group than in MDD-A group and were associated with ATD-induced decreases in testosterone. ATD did not affect anger or cortisol levels.

Conclusion: Depressed patients with anger regulation problems may have greater serotonergic alterations than patients without anger regulation problems. The findings of the present study also suggest that depression and testosterone are associated through serotonergic mechanisms.

Introduction

Symptoms of anger and aggression are very common in patients with major depressive disorder (MDD), even though these symptoms are not part of the diagnostic criteria (Van Praag, 2001). In the early nineties, Van Praag proposed an angry/anxious subtype of depression which is primarily characterized by anxiety and aggression and a low tolerance for stress (Van Praag, 1992). Since then, a number of studies have investigated related phenotypes. For instance, Fava et al. have characterized a subtype of depression based on the presence of anger attacks (Fava and Rosenbaum, 1998, 1999). Anger attacks are defined as sudden spells of anger associated with a surge of autonomic arousal accompanied by symptoms such as tachycardia, sweating, flushing and a feeling of being out of control (Fava et al., 1990). They are present in about 40% of depressed outpatients (Fava et al., 1997, 1993, Fava and Rosenbaum, 1999). Irritability was present in about half of depressed outpatients in two independent studies (Verhoeven et al., 2011, Fava et al., 2009). Both putative subtypes (with irritability or anger attacks) are distinct from MDD without these problems on a number of clinical characteristics including greater levels of anxiety, somatization and suicidality (Fava et al., 2009, Fava et al., 1993, Verhoeven et al., 2011). The clinical relevance of irritability for development of depression was demonstrated in a longitudinal study in adolescents, which showed that irritability at age 15 was a stronger predictor of depression than of delinquency (both assessed at age 17) and that the link between irritability and depression may be largely mediated by common underlying biological mechanisms (Stringaris. et al., 2012).

Alterations in serotonin (5-HT) neurotransmission are a consistent finding in depression, as indicated by various direct and indirect markers of 5-HT function (Maes and Meltzer, 1995, Belmaker and Agam, 2008). Decreased 5-HT function is also present in MDD patients in remission (Smith et al., 1997, Neumeister et al., 2002, Yatham et al., 2012). More pronounced 5-HT alterations have been observed in currently depressed patients with anger attacks (Fava et al., 2000) compared to depressed patients without anger attacks, as indicated by neuroendocrine challenge procedures. 5-HTergic alterations were also observed in in remitted MDD patients with suicidal ideation or behavior during the previous depressive episode (Booij et al., 2002, 2006), as shown by greater symptom responses to Acute Tryptophan Depletion. Whether 5-HT alterations in MDD patients with anger problems persist beyond a depressive episode and how these alterations are associated with anger symptoms and anger-related cortisol and testosterone responses is not known.

The aim of the current study was to test the hypothesis that remitted depressed patients with anger problems during their depression have greater 5-HT impairments than remitted depressed patients without anger problems. 5-HT functioning was induced by acute tryptophan depletion (ATD), a method that transiently lowers plasma concentrations of the precursor of 5-HT, L-tryptophan (Trp). This allows the investigation of the causal effects of

lowered serotonin function in an experimental design (Booij et al., 2003, Delgado et al., 1990, Moreno et al., 2010, Young et al., 1985).

In addition to mood response, we assessed the effects of ATD on two endocrine measures: cortisol and testosterone. Cortisol has been associated with anger problems in MDD (Van Praag, 2002, 1996). Testosterone has frequently been linked to anger and aggression regulation (Archer, 2006, Mehta and Beer, 2009, Persky et al., 1971, Van Honk et al., 1999, Caramaschi et al., 2012). Moreover, both have been shown to interact intensively with the 5-HT system (Cowen, 2002, Strickland et al., 2002, Way and Taylor, 2010, Kuepper et al., 2010, Montoya et al., 2012). Hypothesizing that depressed patients with anger problems are more sensitive to 5-HT alterations than patients without anger problems, we expected that mood and endocrine responses to ATD would be greater in remitted depressed patients with anger problems than in remitted depressed patients without anger problems.

Methods

Participants

Participants were recruited via local mental health institutions and advertisements in local newspapers and university buildings. Inclusion criteria were: age between 18 and 65 years; meeting DSM-IV criteria for past depression; in remission for at least 2 months and a Hamilton Depression Rating Scale (HDRS; Hamilton, M., 1960) score < 10 or Montgomery Åsberg Depression Rating Scale (MADRS;(Montgomery, S. A. and Åsberg, M., 1979) score < 12. Exclusion criteria were: major physical illness; substance abuse and/or dependence within the last 3 months; lifetime psychosis; pregnancy, lactation.

High-dose and low-dose ATD

Participants received a 102.5-g (high-dose ATD) or a 25.7-g (low-dose ATD) amino acid (AA) mixture in a counterbalanced, randomized, double-blind crossover design, as in our previous studies (Booij et al., 2006, Merens et al., 2008). A protein-low lunch was served (Booij et al., 2005a, Riedel et al., 1999) at each test session, approximately 3 hours after the intake of the AA mixture.

Measures during the test sessions

Behavior

Symptoms were assessed with the MADRS (Montgomery and Åsberg, 1979) and the HDRS (Hamilton, 1960). Sleep items were omitted. Anger was assessed using the Anger Expression Inventory (Forgays et al., 1997, Spielberger et al., 1983).

Saliva

Saliva samples were collected using Salicaps (2.0 ml, IBL International) at 4 time-points during each testing day (before ingestion of the AA mixture, + 1.5hrs, + 4hrs, + 7hrs). Before each saliva-collection, participants cleared their mouths with water and then had to refrain from eating and drinking for 30 minutes. Saliva samples were stored at -20°C until assayed at the laboratory of biopsychology at the University of Dresden, Germany. Free cortisol and testosterone concentrations in saliva were measured using a commercially available 'Luminescence Immunoassay for the in-vitro-diagnostic quantitative determination of cortisol in human saliva and serum' and 'Luminescence Immunoassay for the in-vitro-diagnostic quantitative determination of testosterone in human saliva and serum' (IBL, Hamburg, Germany), respectively. The intra and interassay coefficients of variance for cortisol was below 8%. The intra and interassay coefficients of variance for testosterone was below 10%.

Amino acids

Venous blood was obtained (10 ml) from all participants using EDTA tubes to assess total plasma tryptophan and the ratio to its other large neutral amino acids (LNAAs) and processed and analyzed as in our previous studies (Booij et al., 2005a;, see also Fekkes et al., 1995). Since the size of the reductions of both tryptophan levels and the ratio of tryptophan to the other amino acids following adequate intake and tolerance of high and low-dose ATD have been well-documented (at 80-90% and 40-50%, respectively) and have relatively small variability (Booij et al., 2006, 2005a, Merens et al., 2008, Spillmann et al., 2001), these manipulation checks were only determined for participants who had vomited during an ATD session.

Procedure

The study was approved by the medical ethics committee of the Leiden University Medical Center (LUMC) and all participants gave written informed consent before the start of the intake session.

After expressing interest in participation, all eligible participants received written information about the study by mail or e-mail. Following a brief telephone interview to verify initial in- and exclusion criteria, patients were invited for an intake session. During this session, the Structured Clinical Interview for DSM-IV (SCID-IV) (First, Spitzer, Gibbon, & Williams, 1995) was conducted to verify past and present psychiatric diagnoses. The MADRS and the HRSD were used to assess depressive symptoms occurring in the past week. Anger status was determined in a clinical interview. This clinical interview consisted of questions regarding anger-related cognitions and behaviors during the participant's depression, based on the Anger Attacks Questionnaire (AAQ) (Fava et al., 1991) and included questions like: 'Did you feel more easily angered or more irritable during your depression?' and 'Did you physically or verbally attack people?'. Participants who reported persistent or repetitive thoughts and feelings of anger during their depressive episodes and who reported at least one example of angry behavior (such as yelling, throwing things or physically attacking others) were assigned to the MDD+A group. Those who denied such cognitions and behaviors were assigned to the MDD-A group. Inter-method reliability of the group classification was confirmed by its association with self-report measures of anger completed during the intake session, including the State Trait Anger Expression Inventory (STAXI; Forgays et al., 1997, Spielberger et al., 1983) and the Buss-Perry Aggression Inventory (Buss and Perry, 1992) (see also: Table 1.). The intake-session was administered as closely to the first ATD session as possible, preferably within two weeks.

For the ATD sessions, participants arrived at the lab in the hospital at 9 AM after an overnight fast. Upon arrival, a blood sample was taken as well as a saliva sample. The MADRS was administered to measure baseline depression symptoms. Patients filled in the STAXI state questionnaire to measure their current anger symptoms. Next, participants ingested the AA-mixture within half an hour. For the next 4.5 hours (+4.5 hours) patients remained in a private research room. Saliva samples were taken 1.5, 4 and 7 hours after the intake of the AA mixture (+1.5 hours, +4 hours, +7 hours, respectively). A cognitive test battery was completed between +4.5 hours and +6 hours (data not described here). Symptoms were re-assessed using the MADRS at +6.5 hours followed by a blood sample. At the end of the session, participants received a snack to facilitate normalization of AA-levels. This procedure was repeated at least one week later; those who had received the high-dose ATD in the first session received low-dose ATD in the second session and vice versa. Each participant received €180 for participation. Both the participant and the researcher were blind for the order of the high- and low-dose ATD. The AA mixture was prepared by the hospital pharmacology department.

Statistical Analyses

Group differences in demographic and clinical characteristics were investigated by means of chi-square tests and univariate analysis of variance (ANOVA) using general linear models (GLMs).

Separate repeated-measures multivariate analyses of variances were conducted to investigate the effects of the two different doses of ATD on mood, anger and psychophysiology in the two different groups. For mood and state anger, intervention (low dose vs. high dose) and time (before ingestion vs. + 7 hours) were the within-subjects factors. Anger status in depression was used as a between-subjects factor. A similar analysis was conducted for the endocrine measures, using the values before ingestion and +7 hours (when Trp levels are expected to be at their minimum) as time factor.

More detailed analyses for the endocrine measures were performed by calculating the area under the curve with respect to the ground (AUCg) as well as the area under the curve with respect to the increase (AUCi). The AUCg and AUCi will provide an indication of hormonal secretion over the day versus the change over time throughout the day, respectively (Pruessner, J. C. et al., 2003). These AUCs were analyzed using ANOVAs to compare the AUCs with anger status as a between subjects factor. Delta-scores for psychophysiology measures and mood at +7 hours vs. before ingestion of ATD mixture (Δ cortisol and Δ testosterone) were also calculated to examine intercorrelations. Testosterone and cortisol values were log10 transformed to achieve normality of the data.

Mood response to high dose ATD was defined as the MADRS score 6 hours after high dose ATD minus the MADRS score just before high dose ATD.

Table 1

Demographic and clinical characteristics of remitted depressed patients with (MDD+A) and without (MDD-A) anger problems during depression

	MDD + A (n = 10)	MDD – A (n = 16)	p	
Age (mean±SD)	26.9±8.1	25.9±9.3	.79	
Sex (male/female)	2/8	6/10	.42	¶
Smoker (yes/no)	2/8	4/12	> .99	¶
Antidepressant use (yes/no)	5/5	4/12	.19	*
Nr. of previous episodes				
single/recurrent	2/8	4/11^	.70	¶
Suicidality (ever; yes/no)	7/3	13/3	.51	¶
MADRS intake (mean±SD)	3.4±4.3	2.8±2.7	.64	
STAXI (mean±SD)				
Trait	22.0±5.5	15.5±4.0	.002	

*Pearson's chi-square test for antidepressant use (yes/no) vs. anger in depression (yes/no)

¶(Fisher's Exact Test)

^ 1 missing value in MDD-A group

Results

Data screening

For an overview of participant enrollment see Figure 1.

Six of the 28 participants who completed the experimental procedures vomited on at least one of the testing days. We excluded one participant who had vomited during the high-dose ATD session based on the fact that she had a decrease of plasma Trp of only 42% on that day, whereas a reduction of 75%-90% is expected for high-dose and 40-50% for low-dose ATD (Krahn et al., 1996, Spillmann et al., 2001 , Booij et al., 2005a, Merens et al., 2008,). In the other participants who vomited during high-dose ATD, the decrease in Trp levels was at least 74%. In another participant, baseline depression scores (MADRS: 18) were higher than the inclusion criteria allowed (MADRS: 12), due to a procedural error. This participant completed both sessions but was left out from the analyses because ATD responses in symptomatic depressed patients are highly variable and bimodal (Booij et al., 2005c). Hence, 26 participants, 10 MDD+A and 16 MDD-A, were included in the analyses.

Demographic and clinical measures

No significant differences on demographic or clinical characteristics other than anger and aggression symptoms were found between remitted depressed patients with and without anger problems during depression (Table 1).

Mood

As hypothesized, high-dose ATD led to a greater increase in depressive symptoms than low-dose ATD [$F(1, 24) = 12.351$, $p = .002$] (see Figure 2). Furthermore, the increase in MADRS-scores during the high-dose ATD condition tended to be larger in the A+ group than in the A- group, as shown by a trend level group by intervention by time interaction [$F(1,24) = 3.53$, $p = .072$]. Specific contrast tests between the conditions showed that high-dose ATD induced a significant increase in MADRS scores [$F(1,24) = 8.50$, $p = .008$] in the MDD+A group only. Since previous studies have shown that the use of 5-HTergic antidepressant medication is predictive of mood response to ATD (Booij et al., 2002, Delgado et al., 1990, Delgado et al., 1999) and some of our patients in the A+ group were on 5-HT antidepressants (although not a significantly higher number than patients in the A- group), a hierarchical multiple regression analysis was performed to investigate the unique contribution of anger problems during depression on mood response to ATD, while controlling for the use 5-HTergic antidepressants. Current 5-HTergic antidepressant medication use was entered in the first

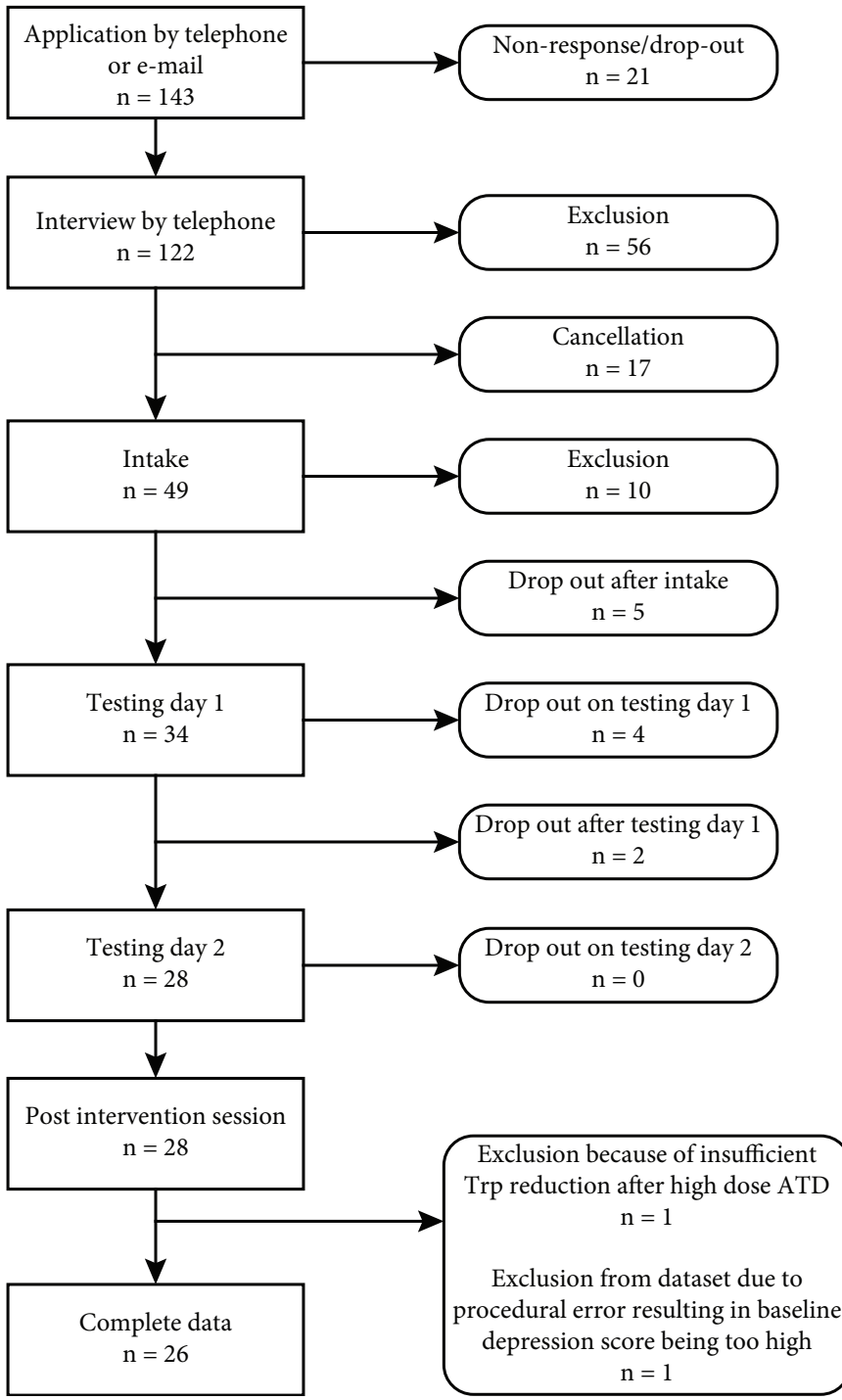

Figure 1
Flow-chart of participant enrollment with drop-out and exclusion rates per phase of the study

block, followed by 'anger problems during depression' in a second block. This analysis showed that anger during depression was associated with mood response to ATD (standardized beta = .455, t = 2.533, p = .019), also when 5-HTergic antidepressant medication was controlled for (standardized beta = .221, t = 1.232, p = .230).

Anger

No effects of intervention, time or intervention by time were found on trait and state anger (STAXI), nor were there any interactions with anger status.

Testosterone

Testosterone levels were significantly lower at +7 hours compared to baseline [$F(1,24) = 17.57$, $p < .001$]. We also found a significant intervention by time interaction. Notably, there was a greater decrease in testosterone levels in the high-dose than in the low-dose condition [$F(1,24) = 6.27$, $p = .019$] (Figure 3). No interaction with anger status was found. No effects of dose, time or dose by time were found on the AUCg or AUCi for testosterone, nor were there any interactions with anger status. The increase in depressive symptoms in the high-dose condition correlated with the decrease of testosterone in the MDD+A group (Pearsons $r = -.72$, $p = .019$). This association was not observed in the MDD-A group (Figure 4a and Figure 4b).

A negative Pearson's r value indicates an association between increases in MADRS scores and decreases in testosterone levels.

Cortisol

Cortisol levels were significantly lower at +7 hours compared to cortisol levels before ATD [$F(1, 24) = 130.98$, $p < .001$]. However, we did not find any interactions with intervention or anger status. No effects of intervention, time or intervention by time were found on the AUCg or AUCi for cortisol, nor were there any interactions with anger status.

Discussion

The current study investigated the effects of low- versus high-dose ATD on mood, testosterone and cortisol in remitted depressed patients who had or had not experienced anger problems during their depression. Consistent with previous studies, high-dose ATD increased depressive symptoms and low-dose ATD did not (Booij et al., 2005a, Merens et al., 2008). In line with our hypotheses, the increase was greater in remitted depressed patients who had

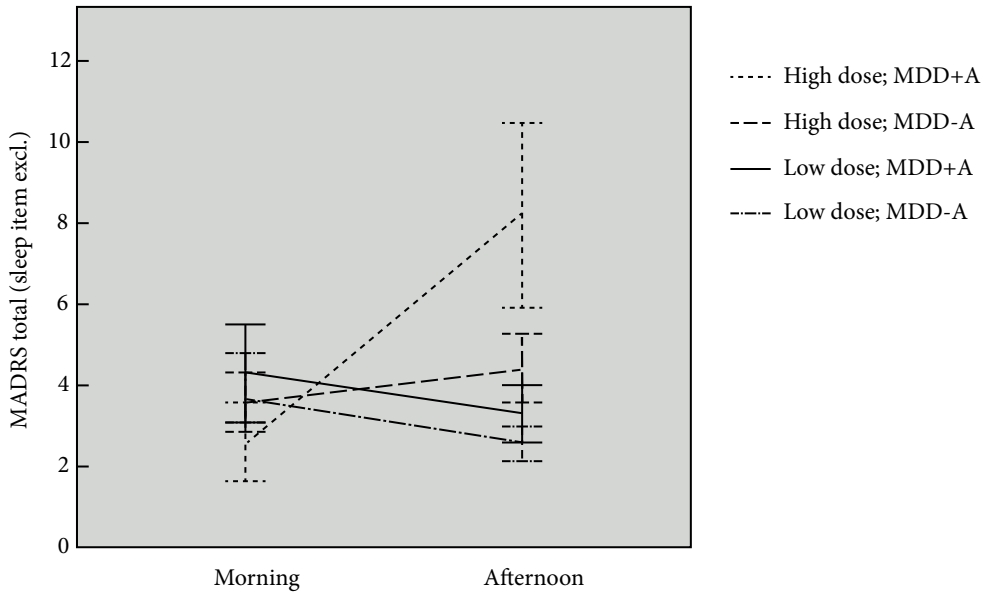

Figure 2
Mood scores before (morning) and after (+6.5h; afternoon) low- and high-dose ATD. Data represent mean-scores ± SE for both MDD+A and MDD-A.

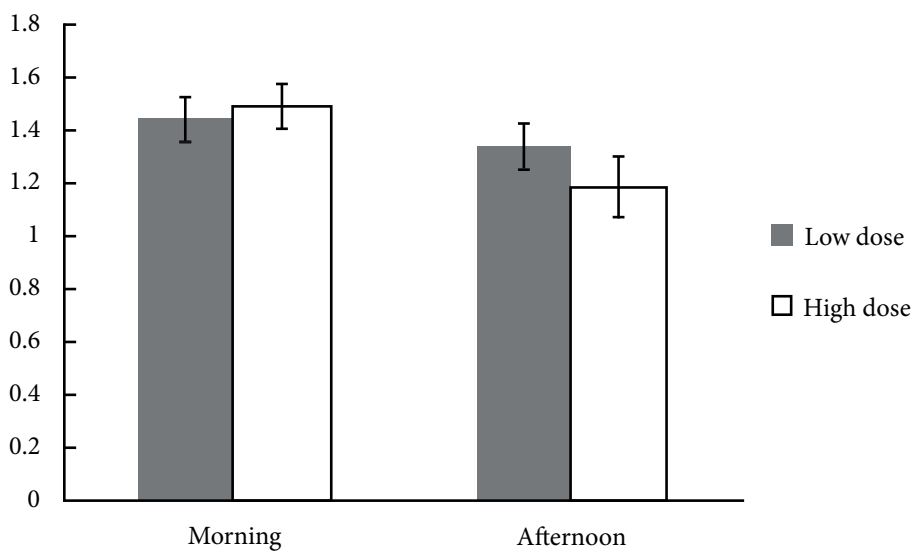

Figure 3
Testosterone levels before (morning) and after (+7h; afternoon) low- and high-dose ATD. Data represent mean-scores ± SE

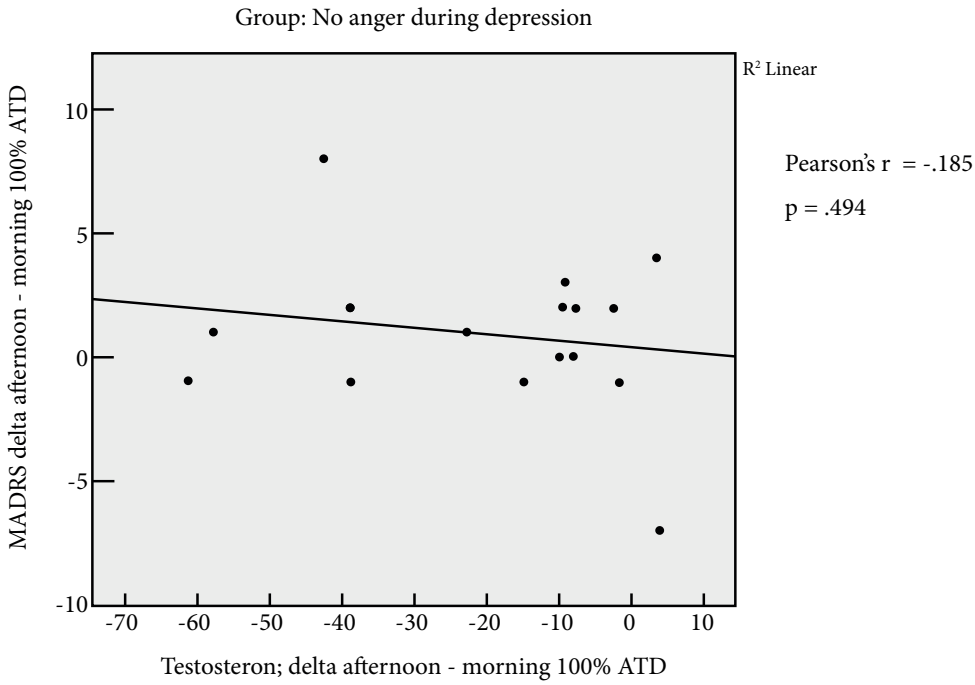

Figure 4a

The correlation between mood response and change in testosterone-levels (Δ testosterone = +7h testosterone levels – morning testosterone levels) in the MDD-A group.

A negative Pearson's r value indicates an association between increases in MADRS scores and decreases in testosterone levels

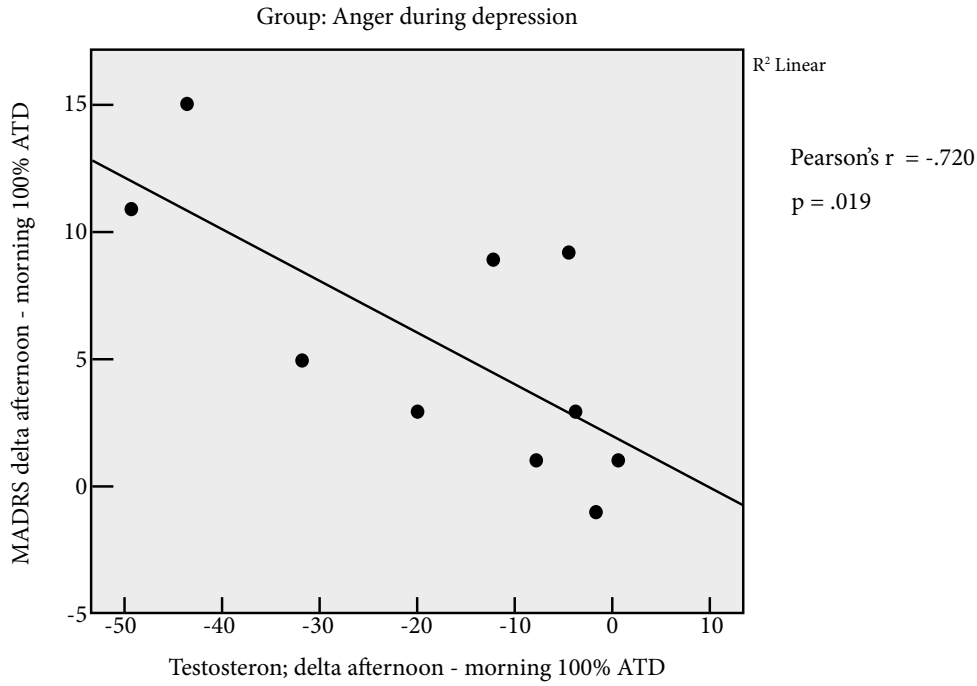

Figure 4b

The correlation between mood response and change in testosterone-levels (Δ testosterone = +7h testosterone levels – morning testosterone levels) in the MDD+A group.

A negative Pearson's r value indicates an association between increases in MADRS scores and decreases in testosterone levels

experienced anger problems (MDD+A) compared to those who had not experienced anger problems (MDD-A).

This greater mood response to ATD in patients whose prior depression had been characterized by impulse dysregulation is in line with previous studies (Booij et al., 2002, Booij et al., 2006, Leyton et al., 2000), showing that mood response to ATD was larger in individuals with strong suicidal ideation during their depression. It is reasonable to assume that the crucial distinction is impulsive behavior, but the current sample size was insufficient to make a direct comparison between patients characterized by anger vs. characterized by suicidality during their depressive episode.

With regard to the endocrine responses to ATD, high-dose ATD significantly lowered testosterone levels at the time that Trp levels were lowest, whereas low-dose ATD did not. In the MDD+A group but not in the MDD-A group, the testosterone response to ATD correlated with mood response to high-dose ATD. The finding that ATD lowers testosterone is consistent with diminished testosterone levels commonly observed in depressed patients (Zarrouf et al., 2009, Giltay et al., 2012). Administration of testosterone may have antidepressant effects in some patients such as older depressed males (Zarrouf et al., 2009). We are not aware of other studies that investigated the effects of ATD on testosterone. The findings of the present study suggest that depression and testosterone are associated through serotonergic mechanisms.

Contrary to our hypothesis, ATD did not increase anger symptoms. Moreover, ATD did not induce the endocrine responses that commonly co-occur with anger such as increased testosterone and cortisol (Harris, 1999, Van Bokhoven et al., 2005). The lack of effects on anger measures suggests that the behavioral response to ATD in remitted depressed patients is primarily expressed in the core symptoms of depression such as low mood and anhedonia (Booij et al., 2005b). These core symptoms may obscure or even counteract an anger response to ATD. In other words, although high-dose ATD affects MDD+A patients to a greater extent than MDD-A patients, anger symptoms may be associated with a different biological mechanism of depression which was not addressed by ATD. Alternatively, the questionnaires may not have been sensitive enough or the laboratory environment may have been too 'neutral' to measure the effects of ATD on anger symptomatology. For future ATD studies in MDD+A patients, it would be of interest to include a provocation task to elicit an anger-response.

The pros and cons of the ATD design using low-dose ATD as the control condition instead of the more often used amino acid mixture containing Trp as placebo, have been discussed previously (Booij et al., 2006, 2005a, Merens et al., 2008). Although the sample size was in line with our other ATD studies in remitted depressed patients, the study would have benefited from a larger sample, especially in the MDD+A group, allowing to investigate higher order interactions between ATD response, anger status and other clinical and demographic

characteristics known to predict mood response, including recurrent depression, suicidality and female sex (Booij et al., 2002). Finally, our patient sample was rather heterogeneous in terms of medication status. Although previous studies have found greater effects of ATD in remitted depressed patients using selective serotonin reuptake inhibitors (SSRI) compared to noradrenergic antidepressant medication (Delgado et al., 1990, Delgado et al., 1999), a reanalysis of several ATD studies showed that other factors such as sex and previous suicidal ideation were better predictors of mood reaction to ATD than the use of medication. This was especially the case for those patients who had already been in remission longer (Booij et al., 2002), as is the case in the current study. Moreover, the MDD+A and MDD-A group did not differ in medication status, neither did the results change when use of medication was controlled for, making it less likely that medication has confounded the results. Nevertheless, it would be of interest to redo the study in an unmedicated sample.

The current study is a first to compare 5-HT function and associated symptom and endocrine responses in patients with and without anger symptoms during their depression, using ATD. In previous studies (Verhoeven et al., 2011, Fava et al., 20010, Fava and Rosenbaum, 1998) it was shown that MDD patients with anger or irritability differ on many behavioral and clinical characteristics. In the present study, we found some indications of greater serotonergic vulnerability in patients whose depression is accompanied by anger symptomatology. Longitudinal studies are needed to further investigate the clinical relevance of our findings in terms of relapse rates and treatment response.

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Chapter 5
Acute tryptophan depletion in remitted depressed patients with and without anger regulation problems: effects on impulsivity and emotion processing

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Paper in preparation

Abstract

Introduction: Anger and irritability occur in up to 40% of depressed patients. Moreover, both depression and anger and irritability have been associated with serotonergic (5-HT) function. The aim of the present study was to investigate serotonergic mechanisms in relation to impulsivity and anger-related emotion-cognitive processes in depression, using acute tryptophan depletion (ATD). More specifically, we investigated the effect of ATD on impulsivity and emotion processing in remitted depressed patients with anger regulation problems during their depression (MDD+A) versus remitted depressed patients without anger regulation problems (MDD-A).

Methods: 10 MDD+A and 16 MDD-A participants (8 male, 18 female, mean age±SD: 26.3±8.7) received a 102.5-g (high dose ATD) and a 25.7-g (low dose ATD) amino acid mixture in a counterbalanced, randomized, double-blind crossover design. Cognitive tasks included the Immediate Memory Task (IMT) and GoStop task for impulsivity and the Facial Expression Recognition Task (FERT) and Approach Avoidance Task (AAT) for emotion processing. All tasks were measured after both low and high dose ATD and compared to a baseline measurement.

Results: On the IMT, we found a decrease in impulsivity after low dose ATD for all participants. We also found a decrease in the discrimination of target stimuli from other stimuli after low dose ATD for all participants (i.e. an increase of commission errors), but no further significant changes in either impulsivity or discriminability after high dose ATD. No differences in impulsivity between MDD+A and MDD-A were found, nor were there any interactions of anger status with ATD. No effects of intervention, anger status or any interactions were found on the emotion processing tasks.

Discussion: Using ATD, the current study did not provide strong support for the involvement of serotonergic mechanisms in impulsivity and processing of emotional faces in depression. Results might be (partly) explained by individual clinical differences in disease course or treatment or by task sensitivity. These factors should be taken into account in future studies.

INTRODUCTION

Up to 40% of patients with major depressive disorder (MDD) experience some form of anger-related problems (Van Praag, 2001), ranging from irritability (Perlis et al., 2009, Fava et al., 2009, Verhoeven et al., 2011) to anger attacks (Fava et al., 1997, Fava et al., 1993, Fava and Rosenbaum, 1999). Patients with MDD and irritability or anger attacks differ from MDD patients without these problems on a number of clinical characteristics, including more severe anxiety, somatization and suicidality and a higher cognitive reactivity to sad mood (Fava et al., 2009, Fava et al., 1993, Verhoeven et al., 2011). In order to investigate one of the underlying biological mechanisms of this putative subtype, we used Acute Tryptophan Depletion (ATD) to lower serotonin (5-HT) function temporarily, thereby aiming to identify the causal role of 5-HT in the development of anger in depression. As discussed in Chapter 4 of this thesis, remitted depressed patients with anger regulation problems during their previous depressive episode (MDD+A) had a more pronounced mood response to ATD than remitted depressed patients without these problems (MDD-A). This suggests that the MDD+A group is more sensitive to 5-HT alterations than the MDD-A group.

Lower 5-HTergic function is also associated with impulsivity, although findings from studies using ATD have been mixed. In some studies increased impulsivity was observed in response to ATD in healthy participants (Crean et al., 2002, Dougherty et al., 2010, Walderhaug et al., 2002), but not in others (Chen and Bargh, 1999, Clark et al., 2005, Evers et al., 2006). One study found that sex moderates the response to ATD, with an increase of impulsivity in men and a decrease in women (Walderhaug et al., 2010). ATD in remitted depressed patients increased impulsivity, but only in a subgroup characterized by suicidal ideation during their prior depression (Booij et al., 2006).

Not only impulsivity is associated with depression; depressed patients also show a bias towards negative information as indicated by various cognitive tasks (Gur et al., 1992, Burt et al., 1995, Bouhuys et al., 1999, Elliott et al., 2011, Gotlib and Mccann, 1984, Gollan et al., 2008, Mikhailova et al., 1996, Segal et al., 1995, Surguladze et al., 2004). This bias partly persists after remission from depression (Bhagwagar et al., 2004, de Raedt and Koster, 2010, Hayward et al., 2005, Joormann and Gotlib, 2007). Remitted depressed patients have shown some persisting bias for emotional stimuli such as fearful faces in response to high dose ATD (Merens et al., 2008b), but another study by Merens et al. (2008a) suggests that biases found during depression may have become latent and will only be active after being triggered. The study by Merens et al. (2008a) found a bias for fearful faces in remitted depressed patients, but only after high dose ATD. Other studies using ATD also found evidence for a role of 5-HT in these emotional biases (Munafò et al., 2006, Elliott et al., 2011, Hayward et al., 2005, Booij et al., 2005c).

One model that links 5-HTergic function and cognitive changes in depression is the two-mode model of depression proposed by Carver et al. (2008). This model states that decreased levels of 5-HT can result in loss of effortful control over reactive systems of approach of reward and avoidance of punishment. What happens when 5-HT decreases and effortful control is lost, depends on which system is most dominant at that time. The result can be either increased avoidance of cues associated with punishment, as is the case in depression, or increased reward approach, resulting in impulsivity. In light of this model, we expect ATD to increase depressive symptomatology in the both groups, but impulsivity only in the MDD+A group.

The aim of the present study was to investigate serotonergic mechanisms in relation to impulsivity and emotional face processing, including those relevant for anger regulation, using ATD. We examined remitted depressed patients with and without anger regulation problems during their depression. We hypothesized that ATD would increase impulsivity in MDD+A but not in MDD-A. Based on the results of one of our previous ATD studies in remitted MDD patients (Merens et al., 2008a), we also hypothesized that high dose ATD would alter the recognition of sad and fearful faces in both MDD groups. In the present sample, we further expected that MDD+A patients would be faster in the processing of angry faces, consistent with their clinical profile. Specifically, we expected the MDD+A group to approach angry faces more often compared to avoidance of angry faces in the MDD-A group.

Methods

Participants

Participants were recruited via local mental health institutions and advertisements in local newspapers and university buildings. Inclusion criteria were: age between 18 and 65 years; meeting DSM-IV criteria for past depression; in remission for at least 2 months and a Hamilton Depression Rating Scale (HDRS Hamilton, 1960) score < 10 or Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) score < 12, the same as in our previous studies (Booij et al., 2006, 2005a). Exclusion criteria were: major physical illness; substance abuse and dependence within the last 3 months; lifetime psychosis; pregnancy, lactation.

During intake, anger status was determined in a clinical interview, which consisted of questions regarding anger-related cognitions and behaviors during the participant's depression, based on the Anger Attacks Questionnaire (AAQ) (Fava et al., 1991) and included questions like: 'Did you feel more easily angered or more irritable during your depression?' and 'Did you physically or verbally attack people?'. Participants who reported persistent or repetitive thoughts and feelings of anger during their depressive episodes and who reported at least one

example of angry behavior (such as yelling, throwing things or physically attacking others) were assigned to the MDD+A group. Those who denied such cognitions and behaviors were assigned to the MDD-A group. Inter-method reliability of the group classification was confirmed by its association with self-report measures of anger completed during the intake session, including the State Trait Anger Expression Inventory (STAXI; Forgays et al., 1997, Spielberger et al., 1983) and the Buss-Perry Aggression Inventory (Buss and Perry, 1992) (see also: Table 1. in Chapter 4).

High dose and low dose ATD

Participants received a 102.5-g (high dose ATD) or a 25.7-g (low dose ATD) amino acid (AA) mixture in a counterbalanced, randomized, double-blind crossover design, as in our previous studies (Booij et al., 2006, Merens et al., 2008a). A protein-low lunch was served (Booij et al., 2005a, Riedel et al., 1999) at each test session, approximately 3 hours after the intake of the AA mixture.

Cognition

Impulsivity

IMT

The Immediate Memory Task (IMT) (Dougherty et al., 2003, Dougherty et al., 2002) used was derived from the continuous performance task (CPT) (Cornblatt et al., 1988). In this 10-minute task, series of five-digit numbers were presented consecutively on the computer monitor for 500 ms with a 500 ms inter-trial interval. Participants were instructed to respond by mouse click to each series identical to the one that preceded it. Three main dependent variables were obtained: 1) correct detections, 2) commission errors, where the participant incorrectly responded to a 5-digit number that differed from the preceding number by only one digit, 3) response latencies, which is the time in milliseconds between stimulus presentations and the participant's recorded responses. The IMT is used to measure the impulsivity of response initiation. Several dependent measures for this task were calculated: the parametric and non-parametric measures for Discriminability (d', A') and Response Bias (β, β"d) as well as the IMT Ratio, which is the proportion of commission errors relative to the correct detections (Dougherty et al., 2009, Dougherty et al., 2002). Discriminability represents the discrimination of target stimuli from other stimuli; Response Bias is the index of impulsive versus cautious decision-making. Since our main interest was impulsivity and we expected results to be distributed normally, our main variable of interest was the parametric measure of Response Bias β.

GoStop

The GoStop was used to measure response inhibition. Series of 5-digit numbers were displayed for 500 msec with a 1500 msec inter-stimulus interval. Like the IMT described above, 5-digit numbers appeared in series, and some of these series were identical to the immediately preceding 5-digit series. Participants were instructed to respond to these matching numbers (the 'go' signal). However, some of these matching series were first presented in black and would then turn red. This was the 'stop signal', and participants were instructed to withhold their response to series turning red. The timing of these stop signals varied across the testing session (50, 150, 250 and 350 ms). The two dependent measures of interest for this task were: 1) correct responses, 2) response inhibition failures, where the participant failed to withhold responding to a matching number when a stop signal had appeared. The primary dependent measure was the GoStop Ratio, which was calculated as the number of response inhibition failures (i.e. incorrect responses to stop trials) relative to the number of correct responses (i.e. go trials). Data from the 150 ms stop delay typically provide the best group discrimination (Marsh et al., 2002). The GoStop task is used to measure the inhibition of an already initiated response.

Emotional processing

FERT

The Facial Expression Recognition task (FERT) measured the ability to detect emotions (Joormann and Gotlib, 2006). Pictures from the Ekman-database (Ekman and Friesen, 1976) of four basic emotions – happiness, sadness, anger and fear – were morphed from a neutral expression to the full expression of an emotion in increments of 2%. For each emotion, one male and one female face were used. Presenting each face for 500ms, a movie-like representation of the transition between neutral and emotional facial expression was created. Participants were instructed to react to the stimuli by pressing a key as soon as they recognized the emotion, after which they had to indicate which of the four emotions they had recognized. As primary outcome measures we looked at average reaction time (expressed by the average Intensity at which an emotion was recognized) and correct responses (Accuracy) for each emotion, especially sad and fearful faces.

AAT

In general, negatively valenced stimuli (e.g. fearful faces) are associated with avoidance behavior and positively valenced stimulus (e.g. smiling faces) are associated with approach behavior (Chen and Bargh, 1999). However, although anger is seen as a negative emotion,

one previous study showed angry faces to elicit approaching behavior (Horstmann, 2003). To measure approach/avoidance reactions to emotional stimuli, the Approach Avoidance Task (AAT) (Heuer et al., 2007) was administered. During this task, participants were asked to respond to either light yellow or grey-colored angry, happy, disgusted or neutral faces. Participants were asked to push away the yellow faces and pull the grey faces towards them using a joystick. Faces increased in size when the joystick was pulled and decreased in size when the joystick was pushed away, disappearing upon complete execution of the correct response.

Outcome measures were the AAT effect scores or AAT ratios (reaction time (RT) push – RT pull) for movement initiation (RT1) and movement completion (RT4) calculated separately for each emotion; this way, positive scores reflected relative approach and negative scores reflected relative avoidance of a certain emotion.

Procedure

The study was approved by the medical ethics committee of the Leiden University Medical Center (LUMC) and all participants gave written informed consent before participation. Remitted depression was established through conduction of the Structured Clinical Interview for DSM-IV (SCID-IV) (First, Spitzer, Gibbon and Williams, 1995) during an intake session. At the end of the intake session, participants performed the cognitive tasks. On testing days, venous blood was taken in the morning and +6h after ATD. Mood was assessed before ATD as well as +6.5h after ATD. The cognitive tasks (IMT, GoStop, FERT and AAT) were administered +4.5h after ATD. Order of high and low dose ATD was counter-balanced over all participants.

Statistical analysis

Group differences in demographic and clinical characteristics were investigated by means of chi-square tests and univariate analysis of variance (ANOVA) using general linear models (GLMs).

The effects of ATD on impulsivity and emotional processing were investigated using GLM for repeated measures, with Intervention (baseline vs. low dose vs. high dose) as within-subjects factor and group (MDD+A/MDD-A) as between-subjects factor. We used contrast tests to investigate specific differences between interventions. For the emotion processing tasks we added emotions as within subjects factors (for the FERT: happy, sad, angry and fear; for the AAT: happy, angry, disgust and neutral). Baseline for all measures was defined as the mean of the intake and the post-intervention session and was used to control for learning effects that

might have occurred as a result of repeated administration of the tasks (cf. Booij et al., 2005b). Because of its non-normal distribution, accuracy (ACC) scores of the FERT were analyzed using nonparametric Friedman's tests.

Results

Data screening

A total of 28 participants completed all measurements (intake, low and high dose ATD testing day and a post-intervention session). As described in Chapter 4 of this thesis, we excluded two participants afterwards; one because of insufficient decrease of Trp levels after high dose ATD and the other because of a procedural error (i.e. a MADRS-score higher than allowed by inclusion criteria).

For two cognitive tasks, intake data for one participant were missing and post-intervention data were used as a baseline. Three participants missed the post-intervention session (over two tasks) and intake data were used as a baseline.

A more detailed overview of participant enrollment can found in Chapter 4 of this thesis, Figure 1.

Participants

No significant differences on demographic or clinical characteristics other than anger and aggression symptoms were found between remitted depressed patients with and without anger regulation problems during depression (Table 1, Chapter 4).

Symptoms

High dose ATD transiently increased depressive symptoms but low dose ATD did not. Symptoms of anger and aggression were however not affected by either high or low dose ATD in both groups. See Chapter 4 for more details.

Impulsivity

Results for the cognitive tasks are summarized in Table 2.

IMT

See also Figures 1a and 1b.

There was a main effect of intervention on measures of Response Bias B [$F(2,48) = 5.27$, $p = .008$] and B"d [$F(2,48) = 5.35$, $p = .008$] as well as of Discriminability d' [$F(2,48) = 11.37$, $p < .001$] and A' [$F(2,48) = 10.49$, $p < .001$] but not on IMT Ratio. Subsequent contrast tests showed a significant increase in Response Bias between baseline to low dose ATD for both β [$F(1,22) = 8.87$, $p = .007$] and B"d [$F(1,22) = 7.94$, $p = .01$], followed by a trend decrease again for high dose compared to low dose ATD, for both measures β [$F(1,22) = 3.12$, $p = .091$] and B"d [$F(1,22) = 3.51$, $p = .075$]). Discriminability differed significantly between from baseline and low dose ATD, being lower after low dose ATD than on baseline, but was also lower after high dose ATD compared to baseline and in high dose ATD compared to low dose ATD d' (respectively: [$F(1,22) = 8.70$, $p = .007$], [$F(1,22) = 16.23$, $p = .001$] and [$F(1,22) = 4.30$, $p = .05$]. The same pattern was visible for A'; baseline vs. low dose ATD: [$F(1, 22) = 5.57$, $p = .028$], baseline vs. high dose ATD: [$F(1,22) = 11.76$, $p = .002$] and low dose ATD vs. high dose ATD [$F(1,22) = 4.49$, $p = .046$]. No main effects of anger during depression nor any interaction effects of anger group (MDD+A/MDD-A) with IMT measures were found.

GoStop

There were no effects of intervention or anger or interaction effects on any of the GoStop outcome measures ($p>0.58$).

Emotional processing

FERT

We found a main effect of emotion, with a significantly faster recognition of happy faces compared to sad faces [$F(1,22) = 105.33$, $p < .001$] as well as significantly fewer mistakes on happy faces compared to sad faces [$F(1,22) = 36.94$, $p < .001$]. Moreover, fear was recognized faster than sadness [$F(1,22) = 5.54$, $p = .028$]. However, there were no main effects of intervention or anger or higher order interaction effects on any of the FERT outcome measures.

AAT

There were no main effects of intervention or group or higher order interaction effects on any of the AAT outcome measures ($p>.34$).

Table 2

Means (SE) of the different cognitive measures as a function of intervention and group.

	MDD + A (n = 10)			MDD – A (n = 16)		
	Baseline	Low dose	High dose	Baseline	Low dose	High dose
IMT						
Discriminability						
d'	2.01 (0.17)	1.65 (0.19)	1.45 (0.19)	1.80 (0.18)	1.61 (0.15)	1.58 (0.16)
A'	0.88 (0.02)	0.85 (0.02)	0.82 (0.03)	0.87 (0.02)	0.85 (0.01)	0.84 (0.02)
Response Bias						
β	0.52 (0.12)	0.73 (0.14)	0.75 (0.15)	0.84 (0.12)	1.15 (0.12)	0.85 (0.10)
β''d	-0.55 (0.14)	-0.33 (0.15)	-0.32 (0.17)	-0.19 (0.11)	0.04 (0.11)	-0.21 (0.11)
IMT ratio*	0.35 (0.05)	0.38 (0.05)	0.43 (0.06)	0.31 (0.03)	0.29 (.04)	0.35 (0.04)
GoStop						
Inhibited responses (%)						
50ms delay	86.5 (3.4)	88.5 (2.8)	88.0 (3.1)	87.8 (4.5)	89.1 (3.5)	85.6 (4.2)
150ms delay	67.0 (4.3)	66.5 (5.7)	67.5 (4.8)	62.8 (5.5)	60.0 (6.0)	63.4 (6.0)
250ms delay	40.5 (3.6)	37.0 (6.8)	47.0 (5.7)	35.9 (4.8)	35.9 (4.8)	35.9 (4.1)
350ms delay	20.5 (3.3)	17.0 (3.3)	25.0 (5.9)	19.7 (2.6)	20.3 (4.0)	18.8 (3.6)
GoStop ratio 150ms**	0.049 (.008)	0.048 (.008)	0.050 (.008)	0.050 (.007)	0.057 (.009)	0.051 (.008)

Table 2 (Cont.)

	MDD + A (n = 10)			MDD – A (n = 16)		
	Baseline	Low dose	High dose	Baseline	Low dose	High dose
FERT						
Intensity (%)						
Happy	27.3 (3.1)	26.1 (2.9)	28.6 (3.7)	26.6 (1.9)	29.2 (1.7)	27.7 (2.2)
Sad	41.7 (4.0)	44.0 (5.1)	41.3 (4.8)	41.7 (3.2)	44.6 (3.0)	43.6 (3.5)
Angry	38.9 (4.4)	40.7 (4.7)	41.8 (5.9)	39.7 (2.6)	42.8 (2.4)	41.8 (2.4)
Fear	37.3 (3.6)	39.1 (3.6)	38.0 (5.0)	39.6 (2.0)	40.2 (2.5)	42.0 (2.0)
Accuracy (average nr correct)						
Happy	9.8 (0.2)	9.8 (0.1)	9.5 (0.2)	9.6 (0.3)	9.3 (0.4)	9.6 (0.3)
Sad	8.8 (0.5)	8.2 (0.6)	7.8 (0.6)	8.0 (0.3)	7.8 (0.6)	7.9 (0.4)
Angry	8.3 (0.5)	8.1 (0.5)	7.9 (0.6)	7.6 (0.4)	7.4 (0.6)	7.8 (0.4)
Fear	8.4 (0.3)	8.2 (0.2)	8.0 (0.6)	7.8 (0.6)	7.5 (0.6)	8.3 (0.6)

Table 2 (Cont.)

	MDD + A (n = 10)			MDD – A (n = 16)		
	Baseline	Low dose	High dose	Baseline	Low dose	High dose
AAT						
Response initiation (ms)						
AAT-ratio RT1 Happy	-14.6 (22.7)	12.5 (15.2)	10.3 (16.5)	-27.6 (15.9)	-9.3 (16.6)	16.0 (16.7)
AAT-ratio RT1 Angry	23.1 (23.1)	-5.1 (16.1)	-8.7 (9.9)	12.7 (17.7)	7.2 (14.1)	16.5 (20.0)
AAT-ratio RT1 Disgust	41.3 (10.5)	12.4 (22.2)	25.6 (10.7)	-4.3 (17.9	-2.5 (11.9)	-4.1 (11.4)
AAT-ratio RT1 Neutral	-4.0 (16.8)	11.5 (14.2)	43.7 (14.7)	6.4 (16.9)	-9.3 (14.2)	6.4 (16.2)
Total response time						
AAT-ratio RT4-RT1 Happy	2.6 (5.8)	-3.9 (15.8)	-5.5 (5.2)	-16.5 (11.6)	-8.2 (9.6)	5.7 (9.1)
AAT-ratio RT4-RT1 Angry	2.6 (2.6)	-2.8 (12.0)	-0.6 (8.2)	-3.9 (8.9)	-25.7 (31.3)	15.3 (6.1)
AAT-ratio RT4-RT1 Disgust	-8.7 (9.9)	23.5 (9.3)	1.1 (6.7)	15.5 (7.8)	-8.8 (7.9)	3.6 (8.6)
AAT-ratio RT4-RT1 Neutral	-0.4 (5.6)	17.5 (10.6)	6.4 (7.2)	1.2 (6.4)	5.8 (11.2)	12.0 (9.2)

* Ratio = Proportion of commission errors to correct detections.

** Ratio = nr of inhibition failures / total nr of go trial responses

MDD+A = remitted depressed patients with anger-problems during their depression
MDD-A = remitted depressed patients without anger-problems during their depression
IMT = Immediate Memory Task
FERT = Facial Expression Recognition Task
AAT = Approach Avoidance Task

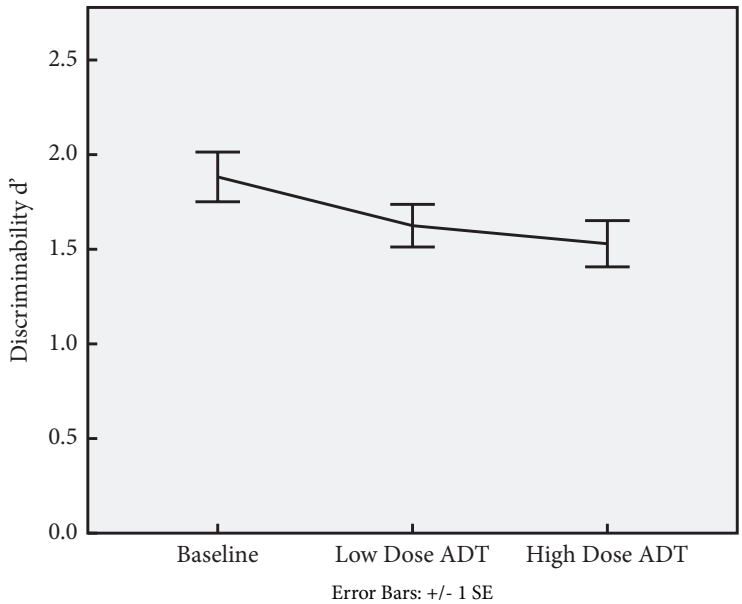

Figure 1a

Discriminability scores d' on Baseline, after low dose ATD and after high dose ATD. Data represent mean-scores ± SE for all participants taken together.

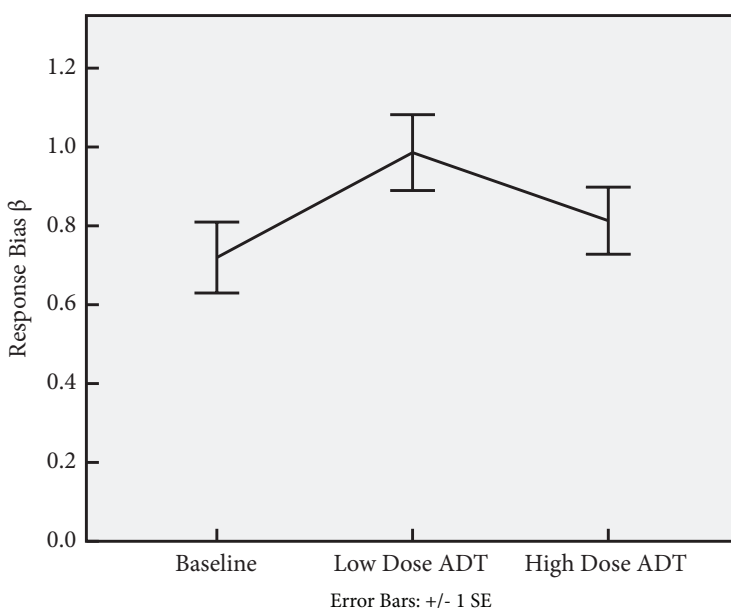

Figure 1b

Response Bias scores β on Baseline, after low dose ATD and after high dose ATD. Data represent mean-scores ± SE for all participants taken together.

DISCUSSION

The current study investigated the effect of high and low dose ATD on impulsivity and processing of emotional faces in remitted depressed patients who had (MDD+A) or had not (MDD-A) experienced anger during their depression. We expected to find changes in impulsivity and emotion processing, especially those emotions related to anger regulation, after ATD in MDD+A compared to MDD-A participants.

Our hypothesis that high-dose ATD would increase impulsivity in MDD+A but not in MDD-A could not be supported by our findings. Specifically, we found a decrease in impulsivity in the Immediate Memory Task (IMT) (measured by β) after low dose ATD for all participants, but no difference between the MDD+A and MDD-A group. We also found a decrease in discriminability after low dose ATD for all participants, but no further significant change after high dose ATD, nor any further interactions with anger.

A previous study in healthy participants found that sex moderates impulsivity in response to ATD, with an increase of impulsivity in men and a decrease in women (Walderhaug et al., 2010). However, the current study lacked power to make the same comparison.

Booij et al. (2006) found increased impulsivity after high dose ATD in a group of remitted depressed patients with previous suicidality. In the present study participants were grouped on the basis of anger; comparison of SI+ and SI- (no suicidal ideation during depression) groups was not possible because all but six of our participants belonged to the SI+ group. Our results differ from these previous findings due to the fact that anger and suicidality may represent different 5HT-ergic endophenotypes in depression. Alternatively, differences in medication status between the studies may account for the discrepancy in results; whereas the current sample consisted of both medicated and unmedicated participants, Booij (2006) included only participants using 5-HT antidepressant medication.

Whereas previous studies found decreased recognition of fearful faces after high dose ATD (Merens et al., 2008a, Harmer et al., 2003, Beacher et al., 2011) and increased recognition of disgusted faces after low dose ATD (Merens et al., 2008a), the current study did not find any effects of either low or high dose ATD on emotion processing, nor in the entire group nor between the MDDA+ and MDDA- group. This discrepancy in findings could be due to the heterogeneity of our current sample, both in terms of medication use (9 out of 26 participants were still using antidepressant medication vs. all patients using SSRIs in Merens et al., 2008a), and in terms of comorbid disorders (several participants had 1 or more comorbid disorders such as panic disorder or binge eating disorder). Sampling characteristics caused by recruitment for research into 'depression and anger' are another unknown and possibly

confounding factor in our sample. The current study used yet a different sample than did Harmer et al. (2003), Beacher et al. (2011) and Merens et al. (2008a), who investigated healthy volunteers (Harmer et al., 2003, Beacher et al., 2011) and remitted depressed patients (Merens et al., 2008a), but did not distinguish on anger or suicidality status. This may explain the difference in outcome between those studies and the current one.

The pros and cons of the ATD design using low dose ATD as the control condition instead of the more often used amino acid mixture containing Trp as placebo, have been discussed previously (Booij et al., 2006, Booij et al., 2005a, Merens et al., 2008a). Although the sample size was in line with our other ATD studies in remitted depressed patients, the study would have benefited from a larger sample, especially in the MDD+A group, allowing to investigate higher order interactions between ATD response, anger status and other clinical and demographic characteristics known to predict mood response, including recurrent depression, suicidality and female sex (Booij et al., 2002).

Future studies into the differences between MDD+A versus MDD-A could benefit from the use of anger or stress induction paradigms. In an earlier study by Bjork et al. (2000), ATD led to increased aggression in highly aggressive men compared to non-aggressive men in response to provocation. Using a provocation paradigm in combination with ATD may be more sensitive to detection of cognitive differences between MDD+A and MDD-A. Clinical practice could benefit from knowledge that indicates whether anger-related cognitions could serve as a marker to differentiate between depression subtypes, as well as the relevance of these cognitions for the best choice for and optimal duration of antidepressant treatment.

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Chapter 6
General discussion

Thirty to 40% of depressed patients experience some form of anger regulation problems – from irritability (Fava et al., 2009, Perlis et al., 2005) to anger attacks (Fava and Rosenbaum, 1998, 1999). The aim of the research described in this thesis was to investigate the significance of anger regulation problems in the context of depression and the extent to which the presence of such problems represents a subtype of depression. This may in turn guide treatment.

We investigated anger regulation problems in depression on different levels including behavior and genetic assessments. We also measured clinical characteristics, psychophysiology and cognitive aspects.

In the first study, we investigated psychophysiological and clinical characteristics associated with anger regulation problems in depression. We did this in a large, well-documented sample recruited from a longitudinal cohort study on depression and anxiety (Netherlands Study on Depression and Anxiety; NESDA). Subsequently, we investigated possible genetic mechanisms (i.e. monoamine oxidase A (MAOA)) associated with anger regulation problems in the context of sad mood. We hypothesized that the association between genotype, childhood trauma, and aggression would be different for men and women. We tested this hypothesis in a sample (N = 432) of college students. Finally, we investigated serotonergic (5-HTergic) mechanisms putatively playing a role in anger regulation problems and associated symptomatology in depression. We hypothesized that depressed patients with anger regulation problems have greater 5-HT alterations than depressed patients without these problems. To test this, we used the method of acute tryptophan depletion (ATD) in a sample (N = 26) of remitted depressed patients.

Summary of the main findings

To investigate whether irritable depressed patients can be distinguished on other characteristics (besides irritability), we used data from a large population based cohort study and compared 420 currently depressed patients with irritability to 493 currently depressed patients without irritability (Chapter 2). We found that irritable depressed patients more often had an anxiety disorder and that they scored higher on anxiety symptoms than non-irritable depressed patients. A higher percentage of the irritable depressed patients had attempted suicide and they scored higher on depression severity, as well as on the personality trait Neuroticism. They scored lower on Agreeableness compared to non-irritable depressed patients. After correction for depression severity, we did not find differences between irritable and non-irritable depressed patients on psychophysiology, including measures of HRV, cholesterol and cortisol. Since there were no extensive neurobiological measures of included (e.g. measures of 5-HT), this study does not allow us to be conclusive on psychophysiological/biological differences between depression with and without irritability.

In Chapter 3, we investigated a possible genetic mechanism for aggression occurring in the context of depression in a healthy population. We therefore investigated the association between MAOA genotypic variation and aggressive thoughts and behaviors as trait and as state phenomena in the context of sad mood. We tested whether the low expression variant (as opposed to the high expression variant) of the MAOA genotype was associated with cognitive reactivity to sad mood (CR) and trait aggression. CR is a putative cognitive marker of depression vulnerability. The scale we used contained a subscale measuring Aggression Reactivity (i.e., the tendency to have an increase of aggressive thoughts and behavior during periods of dysphoria). Moreover, we investigated the association between the MAOA genotype and Aggression Reactivity to sad mood, and its interaction with childhood trauma and sex. Women with the high expressing variant of the MAOA gene (MAOA-H) had higher aggression reactivity scores than women with the low expressing variant (MAOA-L). This association was not observed in men. No associations were found between MAOA variant and measures of state and trait anger, nor did we find any evidence for MAOA gene by childhood trauma interactions. The results of the study described in Chapter 3 may suggest that variation in MAOA gene variants might predispose to anger-related behaviors in the context of depression, but only in women.

To investigate differences in 5-HTergic function between depression with and without anger regulation problems, we challenged the 5-HTergic system in remitted depressed patients with and without anger problems during their depression (MDD+A and MDD-A). We used the method of acute tryptophan depletion (ATD) and measured mood response, cortisol and testosterone levels (Chapter 4) as well as emotion processing and impulsivity (Chapter 5).

We found that high-dose ATD transiently increased depressive symptoms and decreased testosterone levels, 7 hours after ATD. Compared to low dose ATD, symptom response to high dose ATD was more pronounced in the MDD+A group than in the MDD-A group. Moreover, symptom increase was associated with an ATD-induced decrease in testosterone in the MDD+A group but not the MDD-A group. ATD did not affect anger nor cortisol levels in either group, nor in the two groups combined (Chapter 4). No differences were found between MDD+A and MDD-A with respect to the effect of ATD on emotion processing or impulsivity (Chapter 5).

Integration of the main findings

Subtype or severity marker?

A subtype of depression can be described based on a number of very different characteristics or combinations of characteristics. These can be clinical or biological features, as long as

the subtype is clinically meaningful in the sense that it informs treatment and/or predicts prognosis.

Our results described in Chapter 2 are similar to findings from previous studies; irritable depressed patients had higher levels of comorbid anxiety as was also reported by Fava et al. (2009) and they reported more loneliness and more suicide attempts (similar to Perlis et al., 2009). Depression with comorbid anxiety disorder is associated with earlier onset of MDD (Fava et al., 2000a) and a relatively and persistently higher level of depressive symptoms (Sherbourne and Wells, 1997). Depressed patients with comorbid anxiety disorder are at greater risk to quit treatment prematurely (Brown et al., 1996). Although both interpersonal psychotherapy and pharmacotherapy were shown to be effective for depression with and without comorbid generalized anxiety disorder (GAD), depressed patients with comorbid GAD took longer to recover (Brown et al., 1996). A third group of patients with depression and comorbid panic disorder showed poor recovery on both aforementioned therapies compared to depressed patients with and without comorbid GAD (Brown et al., 1996). Suicidality in MDD is also associated with slower recovery (Overholser et al., 1987, Wardenaar et al., 2014).

In terms of personality traits, we found lower scores on Agreeableness and higher scores on Neuroticism in irritable depressed patients. With Agreeableness reflecting the maintenance of positive relations with others (Finch and Graziano, 2001) and Neuroticism reflecting a tendency towards negative mood states (Costa and Mccrae, 1980), the scores we found seem to indicate less favorable personality characteristics in irritable depressed patients compared to non-irritable depressed patients. High Neuroticism scores have previously been shown to strongly predict not only new-onset of but also lifetime MDD (Kendler et al., 2006). Moreover, lower Neuroticism scores have been associated with worse treatment outcome (Kennedy et al., 2005, Mulder, 2002).

Taken together, irritable depressed patients are characterized by more comorbid anxiety and higher risk of suicide. Combined with higher levels of loneliness and less favorable personality characteristics, irritable depressed patients seem to have a more disadvantageous clinical profile compared to non-irritable depressed patients. Such a profile may adversely affect speed of recovery and response to treatment.

Definition of depression subtypes has not only focused on behavioral characterization. Moreover, previous studies had found biological differences between depression with and without anger regulation problems (Iosifescu et al., 2007, Fava et al., 2000b, Dougherty et al., 2004). Therefore, we also investigated biological correlates of anger regulation problems in this thesis. We found lower levels of cholesterol in irritable depressed patients compared to non-irritable patients (Chapter 2), although this difference was no longer significant after the inclusion of several covariates, such as depression severity. Hence, it seems that our findings

for cholesterol are possibly explained by the difference in depression severity between the irritable and non-irritable depressed group, although there is little previous literature to support this.

We found no differences between irritable and non-irritable depressed patients on measures of HRV or cortisol.

To experimentally investigate whether remitted depressed patients with anger regulation problems during their depression have greater 5-HT impairments than remitted depressed patients without these problems during their depression, we applied ATD in a group of remitted depressed patients to investigate the difference in 5-HTergic function between depression with (MDD+A) and without (MDD-A) anger regulation problems. In Chapter 3, the MDD+A group is shown to express greater 5-HTergic reactivity by showing a more pronounced symptom-response to high dose ATD compared to the MDD-A group. We also found a decrease in testosterone levels after high dose (but not low dose) ATD for the MDD+A group (Chapter 3) relative to the MDD-A group. This is consistent with diminished testosterone levels previously observed in depression (Zarrouf et al., 2009, Giltay et al., 2012). This finding may suggest that depression and testosterone are associated through 5-HTergic mechanisms, with greater 5-HT impairments in the MDD+A group compared to the MDD-A group, causing a larger decrease in testosterone levels in the former.

On the other hand, no differences between the MDD+A group and MDD-A group were found on the cognitive tasks; not on impulsivity, nor on emotion processing (Chapter 4). It seems that a possible subtype of depression characterized by anger regulation problems does not extend to the 5-HT/depression related areas of cognition we investigated.

Genetic influences may contribute to the development of depression (Kendler et al., 2001, Sullivan et al., 2000) as well as aggression (Gonda et al., 2011, Antypa et al., 2012, Coccaro et al., 1997). MAOA genotypic variation has previously been associated with aggression (Brunner et al., 1993), particularly in association with maltreatment (Caspi et al., 2002, Foley et al., 2004, Huang et al., 2004, Kim-Cohen et al., 2006, Nilsson et al., 2006, Cicchetti et al., 2007, Enoch et al., 2010), although not consistently (Young et al., 2006, Alia-Klein et al., 2008). Compared to prior research, our study is novel in using outcomes measures that do not only include trait aggression and state aggression, but also reactivity of aggression to changes in mood state. We found that women with the high expressing variant of the MAOA gene (MAOA-H) had higher aggression reactivity scores than women with the low expressing variant (MAOA-L). These results of increased aggression reactivity in women were not found for men, nor were there any associations with childhood trauma. However, our study sample consisted of college students and trauma scores were relatively low.

Our results do suggest that the association between the MAOA genotype and aggression depends on the context of the aggression, and differs between men and women. At least in this non-depressed student sample, vulnerability to aggression regulation problems may depend at least partly on genetic variation and sex which is reflected by reactivity of aggressive behaviors/thoughts. The observation that MAOA genotypic variation seems to affect mood-dependent aggression but not state or trait aggression deserves further exploration in future studies including in clinical samples. A recent study showed that the impact of MAOA genotype in the context of adversity is age-dependent (Pingault, 2013). This finding also supports the need for longitudinal investigations.

Previously established subtypes of depression that have been used in clinical practice include melancholic and atypical depression. A study by Lamers et al. (2010) used data-driven analysis methods and identified subclasses of depression very similar to melancholic and atypical depression: one severe, melancholic class (with e.g. decreased appetite, weight loss, and early morning awakening) (46.3 % of the sample), a second severe, atypical class (symptoms e.g. increased appetite, weight gain, and leaden paralysis) (24.6 % of the sample) and a third class with moderate depression (29.1 % of the sample). Lamers' subclasses were also characterized by significant symptomatic and biological differences, with more smokers and childhood trauma in the melancholic class and higher body mass index (BMI) and higher prevalence of metabolic syndrome in the atypical class. The moderately depressed class discerned itself from the others with significantly less depressive symptoms, less comorbid disorders, and better psychosocial functioning. On average these classes showed 76% stability on a two-year follow-up measurement (Lamers et al., 2012). The severe atypical and severe melancholic patients also differed on biological measures: the atypical subclass had significantly higher levels of inflammatory markers, larger waist circumference, and higher BMI as well as higher levels of metabolic syndrome markers. The melancholic subclass had higher cortisol levels. Differential treatment strategies of antidepressant prescription for the aforementioned classes have been in use for quite some time. Atypical depression has been found to respond better to monoamine oxidase inhibitors (MAOIs) (Quitkin et al., 1993, Liebowitz et al., 1988, Nierenberg et al., 1998) than to tricyclic antidepressants (TCAs), whereas melancholic depression responds better to TCAs and serotonin reuptake inhibitors (SSRIs) (Hirschfeld, 1999).

Besides melancholic and atypical depression, another well-established subtype of depression that responds well to specific treatment is Seasonal Affective Disorder (SAD). In most patients, SAD occurs in autumn and winter, subsiding with the increase of daylight-hours in spring and summer (Lurie et al., 2006). Treatment with light therapy has been found the preferred treatment of choice long ago (Rosenthal et al., 1984), with better results compared to fluoxetine (Ruhrmann et al., 1998).

In the latest version of the DSM, the DSM-5, a new mood disorder has been introduced called disruptive mood dysregulation disorder (DMDD; American Psychiatric Association, 2013), which at first glance is not unlike the anger regulation problems under investigation in this thesis. Diagnostic criteria for this disorder include severe and recurrent temper outbursts which are inappropriate for the situation and which have been present for at least 12 months, occurring as frequent as three times a week. Mood between outbursts should be persistently irritable or angry. However, DMDD differs from the anger regulation problems explored in this thesis in that its diagnostic criteria dictate that the outbursts should not exclusively occur during an episode of major depression. Moreover, DMDD cannot be diagnosed in children younger than 6 years or adults (i.e. older than 18 years) and must be observed before the age of 10, whereas in the current thesis we only focused on adults. The addition of DMDD to the DSM-5 was controversial (Copeland et al., 2013, Parens et al., 2010, Stringaris, 2011). The rationale to include a new disorder mainly based on the extended presence of irritability and temper outbursts may have been the prevention of increasing diagnosis of bipolar disorder in children, especially in the US (Stringaris, 2011). However, Stringaris (2011) also emphasized that DMDD needs to be studied more extensively for it to be meaningful in clinical practice, e.g. its overlap with other disorders such as bipolar disorder and attention deficit hyperactivity disorder (ADHD) (Stringaris, 2011). The first studies on this newly classified disorder have only been published recently (e.g. Copeland et al., 2013, Dougherty et al., 2014). These studies both investigated community samples and found 3-month prevalence rates between 0.8% and 8.2% with the highest rates in preschoolers to 6-year olds. Both studies found high frequencies of comorbid psychiatric disorders in those with DMDD. Another study suggested that children with parents with bipolar disorder are more often diagnosed with DMDD (Sparks et al., 2014), suggesting that DMDD may be a precursor of bipolar disorder.

Not only are the aforementioned subtypes distinguished by a distinct symptom or set of symptoms, most of them (i.e. melancholic and atypical depression, SAD) also differentiate on preferred treatment strategy. Can a putative subtype of depression characterized by anger regulation problems be distinguished? Chapter 2 shows that irritable depressed patients are characterized by a more disadvantageous set of symptoms including higher rates of comorbid anxiety, higher suicide risk and less favorable personality characteristics. We found some biological differences between depression with and without anger regulation problems; although we did not find differences on cortisol, cholesterol and HRV (Chapter 2), we did find a difference in testosterone reaction to ATD between remitted depressed patients with and without anger regulation problems during their depression (Chapter 3). More importantly, those with anger regulation problems during their depression showed a greater mood response to high dose ATD (Chapter 3). Combining this greater mood reaction to ATD with the less advantageous symptom/personality profile found in Chapter 2, anger regulation problems seem to signify a more disadvantageous and possibly more severe form

of depression. The question whether it is possible to signify a subtype of depression only based on greater severity remains to be answered however.

Methodological Considerations and Limitations

In the current thesis, anger regulation problems were operationalized in various ways. We have investigated irritability ('feeling irritable more than half of the time' to 'feeling extremely irritable nearly all of the time'), but also anger (defined by persistent or repetitive thoughts and feelings of anger during the depressive episodes and at least one example of angry behavior such as yelling, throwing things or physically attacking others). In Chapter 5, we measured anger regulation problems more indirectly by means of aggression during an episode of mild dysphoria, with questions regarding thoughts of aggression and behavior such as losing one's temper. Other studies have investigated hostility (Bagby et al., 1997) and suicidal ideation (Booij et al., 2006). As already explained in the introduction of this thesis (Chapter 1), aggressive thoughts and behaviors in the context of depression have been observed for a long time; Freud already signified acts of suicidality (Freud, 1917) as depression turned inwards, which results in aggression towards oneself, and Kraepelin even mentioned murder (Kraepelin, 1883), especially towards loved ones, as an extreme example of aggressive behavior during depression. It remains to be investigated whether irritability and anger attacks as well as suicidality and murder in the context of depression signify the same problems, or originate from different mechanisms altogether.

In addition to the methodological limitations already discussed in chapters 2 to 5 of this thesis, is the sample of remitted depressed patients described in chapters 4 and 5. This sample is rather heterogeneous, especially in terms of current use of medication. Several studies found differences in reaction to ATD between patients on different antidepressants such as 5-HTergic and noradrenergic medication (Delgado et al., 1999). However, a reanalysis of several ATD studies showed that sex and previous suicidal ideation were better predictors of the effect of ATD than use of antidepressant medication (Booij et al., 2002). Moreover, in our current sample, we did not find differences in medication use between the MDD+A and MDD-A group. Nevertheless, it would be of interest to replicate the findings in unmedicated patients, or in samples in which medication is randomized.

Another thing to be considered is the method of ATD used in the current study. The method of ATD used in the current study compares a full dose (100% or high dose) of the amino acid mixture used to lower tryptophan to a mixture containing 25% of the same mixture (low dose). The pros and cons of this design compared to the often used amino acid mixture containing Trp as a placebo condition have been discussed previously (Booij et al., 2006, Booij et al., 2005a, Merens et al., 2008). The alternative for the low dose ATD mixture is a mixture containing tryptophan. This method sometimes causes a rise of total tryptophan

levels (between 10% and 500%) (Klaassen et al., 1999, Weltzin et al., 1994), which may affect outcome measures such as depressive symptoms and cognition (Merens et al., 2008, Markus et al., 1998, Schruers et al., 2000). On the other hand, high dose and low dose ATD do not just differ in the degree to which they lower Trp levels but also lower the other amino acids to a different degree. Hence, both control measures have their own pros and cons. Therefore, it may be of interest to investigate both the ATD method used in this thesis and the ATD methods described above and compare possible outcome differences. Lastly, the observation that the effect of high dose ATD on depressive symptoms differs between men and women (Walderhaug et al., 2007, Booij et al., 2005b) is consistent with the observation from positron emission tomography (PET) studies of lower 5-HT synthesis rates in females than in males (Nishizawa, 1997). These findings have to be taken into account when interpreting results of the current study. Women have a more pronounced depressive response to ATD (Booij et al., 2002). However, in the current thesis we conducted separate analyses of co-variance (ANCOVAs) for differences between men and women, with sex as a covariate and we found no effect of sex on hormonal measures (testosterone and cortisol) or cognition, nor were there any differences on measures of aggression between men and women, either at baseline or after ATD.

Future directions

Anger provocation

The current thesis did not find differences between MDD+A and MDD-A patients on tasks measuring impulsivity and emotion processing. However, previous research combined with results from the current thesis does suggest differences between depression with and without anger regulation problems, both clinically and biologically. Whereas the current ATD study did not show aggression or other cognitive changes in reaction to high dose ATD, a previous study (Bjork et al., 2000) did show increased aggression in reaction to ATD in aggression-prone but not non-aggression-prone men during an anger provocation task, in which they were provoked by having money taken from them during a game. Another study showed increased feelings of anger accompanied by increased regional cerebral blood flow (rCBF) in anterior paralimbic regions of the brain after inducing anger in healthy men, using autobiographical narrative scripts of anger provoking situations (Dougherty et al., 1999). Future experimental studies could possibly benefit not only from inducing sad mood, e.g. by lowering 5-HT as was done in our ATD study, but by additionally using a provocation task such as an anger provocation task, or in the context of stressors, such as laboratory stress induction paradigms.

Brain imaging

Another option for future research would be to further investigate 5-HT neurotransmission in specific brain regions involved in emotion regulation and cognition, using imaging methods such as PET or functional magnetic resonance imaging (fMRI). Expanding on the studies by Bjork et al. (2000) and Dougherty et al. (2004, 1999) in healthy individuals using anger induction paradigms, a next step in the investigation of neural processes could be the inclusion of (remitted) depressed patients with and without anger regulation problems. This could shed some light on in brain regions involved in anger regulation problems in depression.

(Epi)genetics

In Chapter 5, we investigated the role of putative genetic factors associated with aggression in a sample of college students. A next step could be the exploration of this genotype in relation to cognitive reactivity in irritable depressed patients and the interaction with life events. Expanding on this, follow-up studies could identify women with this specific genetic variant at baseline and follow them for several years to identify long term risks of this genetic variant, as well as other risk factors such as childhood maltreatment. Since childhood maltreatment scores were generally low in our sample of college students, including a larger sample of maltreated participants would be of interest for future studies.

It would also be of interest to study the underlying molecular mechanisms of aforementioned gene by environment interactions, e.g. by studying DNA methylation processes in specific 5-HT genes (Booij et al., 2013, Wang et al., 2012).

Treatment

As mentioned in Chapter 1, previous research suggests SSRIs may be useful in treating depression with anger regulation problems. The current thesis did not include randomized controlled trials (RCTs) on the use of 5-HTergic antidepressants to treat depression with anger regulation problems, making it something to be considered for future studies. Not only SSRIs would be of interest for future research, but also the use of Trp to increase brain 5-HT. A study by Aan het Rot et al. (2006) showed significant reductions of quarrelsome behaviors and significantly increased agreeableness in healthy individuals after 15 days of Trp compared to placebo.

Although we cannot draw conclusions about treatment preferences for depression with anger regulation problems based on the current thesis or on previous studies, it may be useful to include this symptom in the diagnostics of depression, since it does signify greater depression

severity. The need to recognize all aspects that could influence depression and its treatment ties in with the concept of staging and profiling.

In other areas of medicine, e.g. oncology, the concepts of staging and profiling are used to facilitate diagnosis and treatment (Huijgens, 2012). Staging is the description of the stage of development a disease is in; profiling is the recognition of factors influencing course of and reaction to treatment (Kapczinski et al., 2009). The idea of introducing staging in psychiatry was already suggested by Fava and Kellner (Fava and Kellner, 1993); however, psychosis is the only psychiatric illness in which this construct has been applied completely and successfully so far (Hetrick et al., 2008). That being said, the Multidisciplinary Guideline for depression (Spijker et al., 2013) does take into account a rough estimate of the stage of the depression (duration shorter or longer than 3 months, first/recurrent episode) and some specific symptoms (suicidality, psychosis, melancholic features) are taken into account in treatment decisions. This could be expanded: placing a person on a continuum of the course of illness, recognizing not only full-blown or even severe stages of the disease, but also vulnerability factors such as family history and prodromal phase of the disease. Some evidence has been found that interventions are more beneficial when used earlier (Kupfer et al., 1989) and it has been suggested that detection of subclinical depression should be seriously considered for (early) intervention and/or treatment (Kessler et al., 1997). Early detection would also decrease the burden of the disease on patients (Feightner and Worrall, 1990a, Feightner and Worrall, 1990b). Early recognition of higher severity of a depressive disorder may call for more intensive treatment options, e.g. combining psychopharmacology with cognitive behavioral therapy (De Jonghe et al., 2001, Oestergaard and Moldrup, 2011, Cuijpers et al., 2009).

As mentioned before, the DSM-5 contains a newly classified depressive disorder based on temper outbursts and aggression called DMDD. Future studies may take this new DSM-5 diagnosis into account when investigating anger regulation problems in the context of depression, and investigate its relation to anger regulation problems in adult depression as has been investigated by the current thesis. A previous study on irritability in children had already shown that irritability in adolescents is a predictor of depression and anxiety in later life (Stringaris et al., 2009). The question remains whether DMDD is a precursor to or childhood version of irritable/angry depression in adults, or possibly bipolar disorder (Sparks et al., 2014). Other studies have also suggested that irritability is may be a feature of unrecognized bipolar (spectrum) disorder (Benazzi, 2003, 2010, Benazzi and Akiskal, 2005).

Investigation into this question may eventually contribute to improved recognition of the different stages of depression.

In addition, more extensive profiling could help recognize aspects of depression that predict outcome and treatment response, much like the current labeling of subtypes has been doing,

but taking into account all possible levels of characterization. Ranging from personality and reactivity profiles to biological profiles which are not restricted to 5-HT, but include dopamine (Tye et al., 2012) and noradrenaline (Haenisch and Bönisch, 2011) as well, the identification of additional characteristics of depression can help create a more complete profile of the disease and may thus contribute to better treatment choice.

Conclusion

The current thesis aimed at investigating the significance of anger regulation problems in depression. One of the aims was to investigate to which extent these problems represent a subtype of depression. This thesis suggests that anger regulation problems during depression signify a more severe form of depression. Previous studies suggest pharmacotherapy, more specifically SSRIs, as the treatment of choice for depression with anger regulation problems. RCT studies on the use of SSRIs and Trp could shed further light on the use of 5-HTergic antidepressants in the treatment of depression with anger regulation problems.

The identification of a specific profile of depression characterized by anger regulation problems may strengthen the idea that research should focus on staging and profiling of depression, identifying factors that contribute to severity of the disease require specific treatment.

The relationship of the currently discussed profile of anger regulation problems in depression with DMDD is another topic that needs to be investigated; is DMDD a precursor of or childhood version of anger regulation problems in depression in adults? Or is it related to bipolar disorder in later life?

Moreover, future research could include brain imaging studies to further quantify the specificity of the profile as well as anger induction paradigms to provoke differences between patients with and without anger regulation problems during their depression. Longitudinal research could contribute to the recognition of risk factors for this specific depression profile as well as precursors in childhood and adolescence, while DNA methylation research might shed light on how gene and environment physiologically interact. Taken together, multidisciplinary research into this subject should integrate several areas of expertise in order to fully determine the role of anger regulation problems in depression and specifically focus on how to implement findings in clinical practice.

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Nederlandse Samenvatting

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Maar liefst 15,4% van de Nederlanders heeft op enig moment in hun leven last van depressieve klachten. Hoewel er sinds het ontstaan van de diagnose 'depressie' veel onderzoek naar deze aandoening is gedaan, en er vele behandelingsvormen mogelijk zijn, is herstel vaak een langdurig en intensief proces. Daarnaast blijft volledig of gedeeltelijk herstel voor sommige patiënten zelfs uit.

De diagnose 'depressie' omvat een grote verscheidenheid aan patiënten. Dit komt doordat de diagnose depressie gesteld wordt op basis van de aanwezigheid van vijf van elf beschreven criteria of symptomen. Het gevolg is dat twee patiënten, die vijf volledig verschillende symptomen rapporteren, toch dezelfde diagnose 'depressie' krijgen. Door deze verscheidenheid is het moeilijk gebleken om snel de juiste behandeling voor een individuele patiënt te vinden. Om de verscheidenheid te verminderen en behandelkeuzes doeltreffender te maken, wordt als sinds het ontstaan van de depressiediagnose gezocht naar relevante subtyperingen van depressie.

De relatie tussen depressie en boosheid werd al gelegd door Kraepelin en Freud, aan het eind van de 19e en begin van de 20e eeuw. In de jaren '90 van de 20e eeuw nam de interesse in deze relatie toe. De Nederlandse professor Dr.van Praag suggereerde dat een combinatie van angstsymptomen met boosheid en/of woedeaanvallen een subtype van depressie kenmerkte, en dat deze symptomen veroorzaakt werden door een verstoring van het serotonine-niveau. Behandeling met antidepressiva die invloed hebben op het op het serotonine systeem zouden de klachten snel en effectief verlichten, zo beargumenteerde van Praag. Onderzoekers uit Boston, waaronder professor Dr. Fava en Dr. Perlis, definieerden dit mogelijke subtype verder en noemden het 'depressie met woedeaanvallen', waarbij een woedeaanval werd gedefinieerd als plotseling opkomende woede, die gepaard gaat met symptomen van autonome activatie zoals hartkloppingen en zweten, zoals die bij een paniekaanval worden waargenomen, maar zonder de voor een paniekaanval kenmerkende gevoelens van angst. Experimentele studies naar dit subtype vonden dat depressieve patiënten die last hadden van dergelijke woedeaanvallen een hogere mate van vijandigheid lieten zien, maar ze waren ook angstiger dan depressieve patiënten zonder woedeaanvallen. Daarnaast verschilden de twee groepen fysiologisch van elkaar: depressieve patiënten met woedeaanvallen hadden een hoger cholesterolgehalte en een verhoogd risico op hartfalen.

De onderzoekers in Boston vergeleken niet alleen depressieve patiënten met en zonder woedeaanvallen, maar ze onderzochten ook een mildere vorm van boosheid, namelijk prikkelbaarheid. Uit het onderzoek bleek dat prikkelbare depressieve patiënten naast hun depressie vaker ook een angststoornis hadden dan niet-prikkelbare depressieve patiënten. Tevens hadden prikkelbare depressieve patiënten vaker een zelfmoordpoging gedaan.

In dit proefschrift wordt dieper ingegaan op de relevantie van boosheid in de context van depressie; verschillen depressieve patiënten met en zonder boosheid klinisch van elkaar, maar ook bijvoorbeeld ook op het gebied van cognitie en serotonerge kwetsbaarheid? Kan inderdaad gesproken worden van een subtype van depressie gekenmerkt door boosheid?

In hoofdstuk 2 is gebruik gemaakt van data uit de Nederlandse Studie naar Depressie en Angst (NESDA) om prikkelbare en niet-prikkelbare depressieve patiënten met elkaar te vergelijken.

46% van de 913 geselecteerde depressieve patiënten had last van een redelijke tot hoge mate van prikkelbaarheid. Deze prikkelbare depressieve patiënten scoorden bovendien hoger op depressie-ernst, angst, hypomane symptomen en zij hadden meer last van gedachten gerelateerd aan agressie in reactie op een sombere stemming (ook wel: cognitieve reactiviteit van agressie), waarbij boosheid als een afgeleide van agressie kan worden gezien. De prikkelbare depressieve patiënten verschilden echter niet van niet-prikkelbare depressieve patiënten op fysiologische parameters, zoals cortisol, cholesterol en hartritmevariabiliteit, ook niet na correctie voor de ernst van de depressie. Ook op langere termijn, namelijk na een jaar, werden vergelijkbare verschillen gevonden tussen prikkelbare en niet-prikkelbare depressieve patiënten.

Erfelijkheid lijkt een belangrijke rol te spelen bij het ontstaan en voortduren van psychopathologie. De erfelijkheid van depressie en agressieis reeds uitgebreid bestudeerd. Er is echter weinig bekend over de erfelijkheid van boosheid gerelateerd aan depressie. In hoofdstuk 3 werd een genetisch mechanisme onderzocht dat mogelijk geassocieerd is met boosheid bij depressie. Het onderzoek richtte zich met name op de relatie tussen de genotypische variatie van Monoamine Oxidase A (MAOA) en boosheid en de al eerder onderzochte interactie met jeugdtrauma. Om de rol van het MAOA-gen bij boosheid bij depressie te onderzoeken, werd getoetst of de lage expressie variant van dit gen o.a. geassocieerd is met verschillende maten van boosheid (situatie-specifiek of 'state' versus persoonlijkheidstrek of 'trait'). Daarnaast werd de cognitieve reactiviteit van patiënten gemeten: dit is de mate waarin negatieve denkpatronen geactiveerd worden op het moment dat iemand somber is. In totaal werden van 432 West-Europese studenten DNA afgenomen en het genotype bepaald van het MAOA-LPR polymorfisme voor het MAOA-gen. Het MAOA-genotype bevindt zicht op het X chromosoom, waarbij een onderscheid kan worden gemaakt tussen efficiëntere (H-allel) en minder efficiënte (L-allel) allelen. Deelnemers vulden tevens vragenlijsten in over jeugdtrauma, boosheid en cognitieve reactiviteit. Vrouwen met het MAOA-H allel hadden hogere agressie reactiviteit scores dan vrouwen met het MAOA-L allel. Dit effect werd niet gevonden bij mannen, hoewel de niet-significante bevindingen bij mannen mogelijk het gevolg van de relatief kleine groep zijn. Er werden ook geen effecten van de MAOA genvariant gevonden op boosheid, of interacties van MAOA genvariant met jeugdtrauma. Een beschermend effect van de lage-expressie variant van het MAOA-gen bij

vrouwen op cognitieve reactiviteit van agressie werd eerder al gevonden in tienermeisjes. Het onderzoek beschreven in dit proefschrift geeft aan dat vrouwen met het MAOA-H allel wellicht gevoeliger zijn voor boosheid of agressie wanneer ze in een sombere stemming zijn.

Zowel depressie als agressie zijn eerder in verband gebracht met verminderde serotonine-overdracht. Een volgende stap was dan ook het onderzoeken van serotonerge kwetsbaarheid bij boosheid in depressieve patiënten. Door gebruik te maken van acute tryptofaandepletie (ATD) werd onderzocht of herstellende depressieve patiënten met boosheid tijdens hun depressie meer beperkingen in het serotonine systeem hebben, in vergelijking met herstellende depressieve patiënten zonder boosheid tijdens hun depressieve episode. In hoofdstuk 4 en hoofdstuk 5 wordt ingegaan op de resultaten van dit experimentele onderzoek. Voor dit onderzoek namen 26 herstelde depressieve patiënten met en zonder boosheid tijdens hun depressie deel aan een ATD-studie. Voor deze studie kregen alle deelnemers zowel een hoge als een lage dosering ATD, waarbij zowel de deelnemers als de onderzoekers niet wisten welke dosering op welke testdag genomen werd. De lage dosering bevat 25% van de hoeveelheid die gebruikt wordt in de hoge dosering. Eerder onderzoek met deze methode heeft aangetoond dat de lage dosering geen effect heeft op stemming en cognitie, terwijl dit bij de hoge dosering wel het geval is.

In hoofdstuk 4 wordt ingegaan op de verschillen tussen de deelnemers met en zonder boosheid tijdens hun depressie in reactie op ATD. Tevens werd in het onderzoek ingegaan op de het effect van ATD op veranderingen van testosteron en cortisolniveaus. Deze twee hormonen zijn betrokken bij zowel depressie als boosheid. De ATD zorgde na 7 uur voor een tijdelijke toename van depressieve symptomen alsmede een afname van het testosteron niveau bij de deelnemers. De stemmingsreactie na ATD was groter in de groep patiënten met boosheid tijdens de depressie dan in de groep zonder boosheid. Deze toename van depressieve stemming hing samen met de afname van het testosteronniveau. Boosheid en cortisol-niveau veranderden niet door ATD. Het lijkt er dus op dat depressieve patiënten met boosheid een grotere verstoring van het serotoninesysteem hebben dan depressieve patiënten zonder boosheid, waardoor ze sterker reageren op ATD. Bovendien suggereren de bevindingen in hoofdstuk 4 dat depressie en testosteron verbonden zijn via serotonerge mechanismen. In hoofdstuk 5 werden verschillen in cognitie tussen herstelde depressieve patiënten met en zonder boosheid tijdens hun depressie onderzocht, waarbij gekeken werd of bij depressie met boosheid ook sprake is van een verhoogde mate van impulsiviteit in vergelijking met de MDD-A groep. Bovendien werd onderzocht of boosheid bij depressie de herkenning van en de reactiesnelheid op emotionele gezichtsuitdrukkingen beïnvloedt. Wat betreft de impulsiviteitstaak werd een afname van het onderscheidingsvermogen tussen stimuli na een lage dosis ATD voor alle deelnemers gevonden, maar verder geen wezenlijke veranderingen in impulsiviteit, reactietijden of onderscheidingsvermogen van de aangeboden stimuli na een hoge dosis ATD. Er werden geen verschillen in impulsiviteit tussen de groep met en zonder

boosheid tijdens hun depressie gevonden. Daarnaast werden ook geen verschillen gevonden in reactie op de ATD methode tussen de twee groepen. De gezichtsherkenningstaken lieten geen van beiden significante effecten zien; niet van ATD voor de totale groep deelnemers, noch voor de groepen afzonderlijk of voor een interactie tussen groep en ATD-dosering.

Hoofdstuk 6 omvat een samenvatting van de hoofdstukken 2 tot en met 5 en een algemene bespreking van de studies in dit proefschrift.

De studies in dit proefschrift suggereren dat er bij boosheid tijdens een depressie vooral sprake is van een ernstigere mate van depressie, waarbij meer symptomen voorkomen, vaker een comorbide angststoornis wordt vastgesteld en een grotere kans op suïcidaliteit bestaat. Tevens verschilt depressie met boosheid van depressie zonder boosheid op fysiologische maten zoals testosteron en cholsterol. Zo bezien draagt het vaststellen van een depressieprofiel met boosheid als specifiek kenmerk bij aan de idee dat onderzoek zich moet gaan richten op stagering en profilering van depressie: het identificeren van factoren die bijdragen aan de ernst van de depressie en die specifieke behandeling vereisen. Vervolgonderzoek naar boosheid bij depressie zou zich dan ook verder kunnen richten op de beste behandelstrategie. Toekomstig onderzoek naar depressie met boosheid kan verder aangevuld worden met hersenonderzoek met behulp van beeldtechnieken; zijn er wellicht verschillen in anatomie en neurale activatiteit van de hersenen tussen depressieve patiënten met en zonder boosheid? Een aanvulling op de ATD studie beschreven in hoofdstuk 4 en 5 kan bestaan uit de toevoeging van boosheidinductie, oftewel een experiment, waarin boosheid wordt uitgelokt door middel van een frustrerende taak of het denken aan een situatie waarin men boos was. Wellicht komen cognitieve (en andere) verschillen tussen patiënten met en zonder boosheid tijdens hun depressie dan alsnog aan het licht.

In de nieuwste versie van de 'Diagnostic and Statistical Manual of Mental Disorders' (DSM), de DSM-5, staat een nieuwe stemmingsstoornis beschreven die gekenmerkt wordt door regelmatige woedeuitbarstingen genaamd 'disruptive mood dysregulation disorder' (DMDD). Deze woedeuitbarstingen zijn echter niet exclusief aanwezig tijdens depressieve episodes. Bovendien kan de diagnose niet gesteld worden na het 18e levensjaar. De relatie van het in dit proefschrift besproken profiel van boosheid bij depressie met DMDD is een ander onderwerp dat moet worden onderzocht; is DMDD gedurende de kindertijd een voorloper van boosheid bij depressie bij volwassenen? Is er een verband tussen DMDD en het voorkomen van een bipolaire stoornis in het latere leven? Om beter zicht te krijgen op de ontwikkeling van depressie met boosheid en mogelijke risicofactoren hiervoor, zoals DMDD in de kindertijd, is vervolgonderzoek nodig in de vorm van longitudinale studies. Onderzoek naar verandering in genetische expressie gedurende het leven, veroorzaakt door DNA-methylatie, kan vervolgens nieuw licht werpen op hoe deze risicofactoren vanuit de omgeving interacteren met genen en zo invloed hebben op de ontwikkeling van depressie met boosheid.

Multidisciplinair onderzoek naar dit onderwerp kan een aantal expertisegebieden integreren, om zo te bepalen wat de rol van boosheid bij depressie inhoudt. Uiteindelijk zal dan duidelijk moeten worden hoe de verschillende resultaten een rol in de klinische praktijk en dus de behandeling van de patiënt kunnen spelen.

Dankwoord

Daar is ie dan: het snelst geschreven, en daardoor meest oprechte deel van dit proefschrift. Ik kan namelijk veel alleen, maar dit had ik nooit gekund zonder de hulp van een heleboel mensen.

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Dan. Kipjes. Eigenlijk zijn we wel toe aan een nieuwe titel, anderzijds: kan het ons lekker schelen wat mensen van onze Geuzennaam denken. Aline, Anne, Marieke, Marin: wij, begonnen als 5 promovendi, zo verschillend en steeds verspreid over verschillende steden, provincies en continenten. Dat er nog maar vele kipjesweekenden mogen volgen, met nieuwe én vertrouwde ingrediënten.

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Geachte paranimfen. Mike, van antagonist, naar docent, naar grote broer en vriend. Als paranimf heb jij geen sabel nodig, je maakt me altijd sterker.

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Thus, je bent de enige echte Brabo van ons drieën, en in je beroepskeuze ga je ook je eigen weg. Ik ben een stuk cooler met een DJ als broer. Merel, kleine zus, gelukkig promoveer ik toch nog net iets eerder dan jij, maar wat fijn dat je me kon helpen met de laatste loodjes.

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Lieve pp&mm, behalve een belezen, kritische, rijke basis dank ik aan jullie ook mijn doorzettingsvermogen. Goed voorbeeld doet goed volgen, en ik zal altijd door die zure appel bijten. Dat proefschrift is er dankzij jullie!

Laurens. Sta je dan, op de cover. Meer dan 'fietsbel' hoef ik niet te zeggen toch?

Curriculum Vitae

Floor Verhoeven (12-12-1982) spent the first eighteen years of her life in Breda, the Netherlands. After graduating from the Onze Lieve Vrouwelyceum in 2001, she took a gap-year before starting her BSc in Biological Psychology at the University of Maastricht in 2002. In 2007, she obtained her MSc in Neuropsychology at the same University after which she commenced her PhD research at Leiden University, under the supervision of Prof. Dr. Willem van der Does and Dr. Linda Booij.

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